ANA 2020 Program

Sunday Poster Presentations

Health Services Research

101. Multi-Objective Predictive Control of Covid-19 Epidemics and Mental Health

Abhishek Dutta, PhD. *University of Connecticut, Storrs, CT, USA.*

102. Population-Based Incidence Estimate of Anti-NMDA Receptor Encephalitis in New York City

Anusha K. Yeshokumar, MD[1], *Jacqueline Gofshteyn, MD*[2], *Parul Agarwal, PhD*[1], *Kiran Thakur, MD*[3], *Natasha Basma, MPH*[2], *Mary Claire Tuohy, BS*[3], *Jyoti Ankam, MBBS MPH*[3], *Sarah Torres, MS*[3], *Shelley Varnado, MD*[4], *Britany Klenofsky, MD*[1], *Elissa Yozawitz, MD*[5], *Nicole Luche, BA*[2], *Dale Hesdorffer, PhD*[3], *Aaron Nelson, MD*[4], *Steven Wolf, MD*[1], *Patricia McGoldrick, NP*[1], *Zachary Grinspan, MD MS*[2], *Nathalie Jette, MD MS*[1]. [1]*Icahn School of Medicine at Mount Sinai, New York, NY, USA,* [2]*Weill Cornell Medical Center, New York, NY, USA,* [3]*Columbia University Medical Center, New York, NY, USA,* [4]*NYU Langone, New York, NY, USA,* [5]*Montefiore Medical Center, New York, NY, USA.*

103. Increasing Out-of-Pocket Costs for Privately-Insured Neurology Patients

Chloe E. Hill, MD, MS[1], *Evan L. Reynolds, PhD*[1], *James F. Burke, MD, MS*[1], *Mousumi Banerjee, PhD*[1], *Kevin A. Kerber, MD, MS*[1], *Brandon Magliocco, MS*[2], *Gregory J. Esper, MD, MBA*[3], *Lesli E. Skolarus, MD, MS*[1], *Brian C. Callaghan, MD, MS*[1]. [1]*University of Michigan, Ann Arbor, MI, USA,* [2]*American Academy of Neurology, Minneapolis, MN, USA,* [3]*Emory University, Atlanta, GA, USA.*

104. Patient Travel for Neurologist Visits and Implications for Telemedicine: A US Population-Based Medicare Study

Chun Chieh Lin, PhD, MBA, *Brian C. Callaghan, MD, MS, Lesli E. Skolarus, MD, MS, Chloe E. Hill, MD, MS, Lindsey B. De Lott, MD, James F. Burke, MD, MS, Kevin A. Kerber, MD, MS. Department of Neurology Health Services Research Program, University of Michigan Medical School, Ann Arbor, MI, USA.*

105. Neurological Comorbidities in Hospitalized Patients with Opioid Abuse

Kevin Nelson, MD, Katelyn Dolbec, MD, William Watson, MD, Hanwen Yuan, PhD, ***Mam Ibraheem, MD, MPH****. University of Kentucky-Department of Neurology, Lexington, KY, USA.*

106. Does Socioeconomic Status Predict Fetal Brain Volumes?

Madeline A. Dolins, BS[1], *Valerie Rofeberg, MS*[1], *Reem Chamseddine, BS*[1], *Maggie Mittleman, BS*[1], *Ali Gholipour, PhD*[1,2], *Jane W. Newburger, MD, MPH*[1,2], *Cynthia M. Ortinau, MD, MPH*[3], *David Wypij, PhD*[1,4], ***Caitlin K. Rollins, MD, SM***[1,2]. [1]*Boston Children's Hospital, Boston, MA, USA,* [2]*Harvard Medical School, Boston, MA, USA,* [3]*Washington University in St. Louis, St. Louis, MO, USA,* [4]*Harvard TH Chan School of Public Health, Boston, MA, USA.*

107. Social Factors Related to Home-Based Telerehabilitation after Stroke

Archana Podury, BA[1], *Sophia Raefsky, BS*[2], *Lucy Dodakian, MA, OTR/L*[3], *Vu Le, MS*[3], *Alison McKenzie, PT, DPT, PhD*[3,4], *Jill See, PT, MPT*[3], *Robert Zhou, BA*[3], *Thalia Nguyen, BS*[2], *Benjamin Vanderschelden, BA*[2], *Gene Wong, BS*[2], *Laila Nazarzai, BS*[3], *Jutta Heckhausen, PhD*[3], *Steven C. Cramer, MD, MMSc*[5], *Amar Dhand, MD, PhD*[6]. [1]*Harvard Medical School, Harvard-MIT Health Sciences & Technology Program, Boston, MA, USA,* [2]*University of California, Irvine, School of Medicine, Irvine, CA, USA,* [3]*University of California, Irvine, Irvine, CA, USA,* [4]*Chapman University, Orange, CA, USA,* [5]*University of California, Los Angeles, Los Angeles, CA, USA,* [6]*Brigham and Women's Hospital, Boston, MA, USA.*

108. Twelve-Year Rates and Causes of Admissions among Those with Neurological Conditions in the US: A Nationally Representative Study

Charlotte Solmssen, BA, *Parul Agarwal, PhD, Churl-Su Kwon, MD, MPH, Huaqing Xi, BA, Mandip Dhamoon, MD, DrPH, Madhu Mazumdar, PhD, Nathalie Jette, MD, MSc. Icahn School of Medicine at Mount Sinai, New York, NY, USA.*

109. Understanding and Informing Emergency Cardiovascular Disease Preparedness during the Coronavirus Outbreak among Vulnerable Populations

Maria Cielito Robles, BS[1], *Casey L. Corches, MPH, MSOTR/L*[1], *Morgan Bradford, BS*[1], *Tia S. Rice, MSHE*[1], *Mellanie V. Springer, MD, MS*[1], *Sarah Bailey, MS*[2], *Lesli E. Skolarus, MD, MS*[1]. [1]*University of Michigan Medical School, Ann Arbor, MI, USA,* [2]*Bridges to the Future, Flint, MI, USA.*

110. Monitoring Real-Time Data in a Randomized Clinical Trial through Web-Based Dashboards during Coronavirus Pandemic

Zahera J. Farhan, MPH[1], *Mackenzie Dinh, MS, CCRC*[1], *William Meurer, MD*[1], *Candace Whitfield, BS*[1], *Lesli Skolarus, MD, MS*[2]. [1]*Department of Emergency Medicine, University of Michigan, Ann Arbor, MI, USA,* [2]*Department of Neurology, University of Michigan, Ann Arbor, MI, USA.*

111. Adverse Childhood Experiences in Patients with Neurological Disease

Adys Mendizabal, MD, MA[1], *Cody Nathan, MD*[2], *Marissa Anto, MD, MSc*[3], *Louise N. Breen, BS*[2], *Gloria Young, BSN*[2], *Nabila Dahodwala, MD, MS*[2]. [1]*University of California, Los Angeles, CA, USA,* [2]*Hospital of the University of Pennsylvania, Philadelphia, PA, USA,* [3]*Children's Hospital of Philadelphia, Philadelphia, PA, USA.*

112. Trends in Imaging Utilization and Hospitalization of Dizziness and Vertigo in US Emergency Departments (1995-2015)

Shervin Badihian, MD[1], *Krisztian Sebestyen, MS*[2], *Maningbe Keita, PhD*[3], *Najlla Nassery, MD; MPH*[4], *Zheyu Wang, PhD*[5,6], *David E. Newman-Toker, MD; PhD*[1,7], *Ali S. Saber Tehrani, MD*[1]. [1]*Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA,* [2]*Johns Hopkins University School of Medicine, Department of Surgery, Baltimore, MD, USA,* [3]*Johns Hopkins Bloomberg School of Public Health, Department of Health Policy and Management, Baltimore, MD, USA,* [4]*Johns Hopkins University School of Medicine, Division of General Internal Medicine, Baltimore, MD, USA,* [5]*, Sidney Kimmel Comprehensive Cancer Center, Division of Biostatistics and Bioinformatics, Baltimore, MD, USA,* [6]*Johns Hopkins Bloomberg School of Public Health, Department of Biostatistics, Baltimore, MD, USA,* [7]*Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, MD, USA.*

113. Risk Factors for Diagnosis of Seizure in the Inpatient Stroke Code Population

Danison Emmerson, MD[1], *Karan Topiwala, MBBS*[1], *Lisa Knopf, MD*[2], *Erica Schuyler, MD*[2]. [1]*University of Connecticut - Department of Neurology, Farmington, CT, USA,* [2]*Hartford Healthcare Ayer Neuroscience Institute, Hartford, CT, USA.*

Neurogenetics

114. Schwann Cells with Fig4 Deficiency are Predisposed to Demyelination

Bo Hu, PhD[1], *Daniil Moiseev, BS*[1], *Jun Li, MD, PhD*[1,2]. [1]*Wayne State University School of Medicine, Detroit, MI, USA,* [2]*John D. Dingell VA Medical Center, Detroit, MI, USA.*

115. Loss of CHCHD2 and CHCHD10 Activates Oma1 Peptidase to Disrupt Mitochondrial Cristae Phenocopying Patient Mutations

Derek Narendra, MD, PhD[1], *Yi-Ting Liu, BS*[1], *Xiaoping Huang, MD*[1], *Diana Nguyen, BS*[1], *Mario Shammas, BS*[1], *Beverly Wu, BS*[1], *Eszter Dombi, PhD*[2], *Springer A. Danielle, VMD, DACLAM*[3], *Joanna Poulton, MRCP, DM*[2], *Shiori Sekine, PhD*[4]. [1]*National Institutes of Neurological Disorders and Stroke, Bethesda, MD, USA,* [2]*Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom,* [3]*National Heart Lung and Blood Institute, Bethesda, MD, USA,* [4]*Aging Institute, Division of Cardiology, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA.*

116. An Undiagnosed White Matter Disorders Neurogenetics Clinic

Jennifer Orthmann-Murphy, MD, PhD. *University of Pennsylvania, Philadelphia, PA, USA.*

117. *FTH1De Novo* Dominant Variants Alter Iron Metabolism and Cause a Pediatric Onset Neuroferritinopathy

Joseph T. Shieh, MD PhD[1], *Alonso J. Tintos-Hernandez, PhD*[2], *Adrian Santana, BS*[3], *Joshua A. Bulos, BS*[4], *Camila Berera, MD*[5], *Joanna J. Phillips, MD PhD*[1], *Ivan J. Dmochowski, PhD*[4], ***Xilma R. Ortiz-Gonzalez, MD PhD***[6,3]. [1]*University of California San Francisco, San Francisco, CA, USA,* [2]*The Chidren's Hospital of Philadelphia, Philadelphia, PA, USA,* [3]*The Children's Hospital of Philadelphia, Philadelphia, PA, USA,* [4]*University of Pennsylvania, Philadelphia, PA, USA,* [5]*University of California San Francisco, San Francisco, CA, USA,* [6]*University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.*

118. Early Experience with Hematopoietic Stem Cell Transplant for Adult Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia

Balvinder Singh, PhD, *Shernan Holtan, MD, Troy Lund, MD, Daniel Kenney-Jung, MD. University of Minnesota, Minneapolis, MN, USA.*

119. ADNC-RS, a Clinical-Genetic Risk Score, Predicts Alzheimer's Pathology in Autopsy-Confirmed Parkinson's Disease and Dementia with Lewy Bodies

David L. Dai, B.A., *Tom F. Tropea, D.O., John L. Robinson, B.S., EunRan Suh, Ph.D., Howard Hurtig, M.D., Daniel Weintraub, M.D., Vivianna Van Deerlin, M.D., Ph.D., Edward B. Lee, M.D., Ph.D., John Q. Trojanowski, M.D., Ph. D., Alice Chen-Plotkin, M.D. University of Pennsylvania, Philadelphia, PA, USA.*

120. The Chromatin Remodeling Enzyme Chd4 Regulates Genome Architecture in the Mouse Brain

Jared V. Goodman, PhD[1], *Tomoko Yamada, PhD*[2], *Yue Yang, PhD*[3], *Lingchun Kong, PhD*[1], *Dennis Y. Wu, BS*[1], *Guoyan Zhao, PhD*[1], *Harrison W. Gabel, PhD*[1], *Azad Bonni, MD PhD*[1]. [1]*Washington University in St. Louis School of Medicine, St. Louis, MO, USA,* [2]*University of Tsukuba, Tsukuba, Japan,* [3]*Northwestern University, Chicago, IL, USA.*

121. Prevalence of *RFC1*-Mediated Spinocerebellar Ataxia in a North American Ataxia Cohort

Dona Aboud Syriani, None[1], *Darice Wong, PhD*[1], *Sameer Andani, BS*[2], *Claudio M. De Gusmao, MD*[3], *Yuanming Mao, BS*[1], *May Sanyoura, PhD*[2], *Giacomo Glotzer, None*[2], *Paul*

J. Lockhart, PhD[4], Sharon Hassin-Baer, MD[5], Vikram Khurana, MD, PhD[3], Christopher M. Gomez, MD, PhD[2], Susan Perlman, MD[1], Soma Das, PhD[2], ***Brent Fogel, MD, PhD[1]****. [1]UCLA, Los Angeles, CA, USA, [2]University of Chicago, Chicago, IL, USA, [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, [4]University of Melbourne, Parkville, Australia, [5]Tel-Aviv University, Tel-Aviv, Israel.*

122. A Diagnostic Ceiling for Exome Sequencing in Cerebellar Ataxia and Related Neurological Disorders

Kathie J. Ngo, None[1], Jessica E. Rexach, MD, PhD[1], Hane Lee, PhD[1], Lauren E. Petty, MS[2], Susan Perlman, MD[1], Juliana M. Valera, MS[1], Joshua L. Deignan, PhD[1], Yuanming Mao, BS[1], Mamdouh Aker, BS[1], Jennifer E. Posey, MD, PhD[3], Shalini N. Jhangiani, MS[3], Zeynep H. Coban-Akdemir, PhD[3], Eric Boerwinkle, PhD[3], Donna Muzny, MS[3], Alexandra B. Nelson, MD[4], Sharon Hassin-Baer, MD[5], Gemma Poke, MD[6], Katherine Neas, MBchB[6], Michael D. Geschwind, MD, PhD[4], Wayne W. Grody, MD, PhD[1], Richard Gibbs, PhD[3], Daniel H. Geschwind, MD, PhD[1], James R. Lupski, MD, PhD, DSc[3], Jennifer E. Below, PhD[2], Stanley F. Nelson, MD[1], ***Brent Fogel, MD, PhD[1]****. [1]UCLA, Los Angeles, CA, USA, [2]Vanderbilt University Medical Center, Nashville, TN, USA, [3]Baylor College of Medicine, Houston, TX, USA, [4]UCSF, San Francisco, CA, USA, [5]Tel-Aviv University, Tel-Aviv, Israel, [6]Wellington Hospital, Wellington, New Zealand.*

123. Peripheral Nerve Toxicity of Sulfatide in Metachromatic Leukodystrophy

Christian Krarup, MD[1]*, Christine í Dali, MD[2], Mihai Moldovan, MD[1], Mohamed H. Farah, MD[3], Ingeborg Krägeloh-Mann, MD[4], David AH Whiteman, MD[5], Jing Li, PhD[5], Norman Barton, MD[5], Samuel Gröschel, MD[4]. [1]Department of Clinical Neurophysiology, Rigshospitalet, Copenhagen, Denmark, [2]Department of Clinical Genetics, Rigshospitalet, Copenhagen, Denmark, [3]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA, [4]Department of Neuropediatrics, University Children's Hospital Tübingen, Tübingen, Germany, [5]Shire (a member of the Takeda group of companies), Lexington, MA, USA.*

124. Biodistribution of Spherical Nucleic Acids in the Nonhuman Primate Central Nervous System

Grant T. Corbett, Ph.D.*, Lauren R. Moore, Ph.D., Scott Mix, M.S., Andrew Schook, B.A., SubbaRao Nallagatla, Ph.D., Weston L. Daniel, Ph.D., Leo P. Kelly, Ph.D., Bart R. Anderson, Ph.D. Exicure, Inc., Skokie, IL, USA.*

125. Rapid Identification of Polymicrobial Pathogens Using Nanopore 16s Amplicon Sequencing in the Patients with Brain Abscess

Hyoshin Son, MD[1]*, Jangsup Moon, MD, PhD[2,1], Narae Kim, PhD[1], Seungeun Hwang, MD[1], Sang Kun Lee, MD, PhD[1], Kon Chu, MD, PhD[1]. [1]Deparment of Neurology, Seoul National University Hospital, Seoul, Korea, Republic of, [2]Rare Disease Center, Seoul National University Hospital, Seoul, Korea, Republic of.*

126. Amelioration of Brain Histone Methylopathies by Balancing a Writer-Eraser Duo Kmt2a-Kdm5c

Shigeki Iwase, PhD*. University of Michigan Medical School, Ann Arbor, MI, USA.*

127. Novel Putative TUBB4 Mutation in a Case of Leukodystrophy with Demyelinating Peripheral Neuropathy

Shri K. Mishra, M.D., M.S., ABMS, FAAN, FNAA, FANA[1]*, Shaweta Khosa, M.D.[1], Frank Diaz, M.D.[1], Camille Malatt, M.D.[2], Brent L. Fogel, M.D., Ph.D.[3], Kathie J. Ngo, M.D.[3]. [1]Olive View–UCLA Medical Center, Sylmar, CA, USA, [2]University of California, Los Angeles, Los Angeles, CA, USA, [3]Program in Neurogenetics, Department of Neurology, David Geffen School of Medicine , University of California, Los Angeles, Los Angeles, CA, USA.*

128. Genetic Risk for Elevated BP Predicts 6-Month Blood Pressure Levels after Intracerebral Hemorrhage

Evangelos Pavlos Myserlis, MD[1,2]*, Kay-Cheong Teo, MBBS, FHKAM5[3], Bailey E. Montgomery, BS[1,2], Jessica Abramson, BA[1,2], Lansing Sugita, BS[4,5], Andrew D. Warren, BS[5], Joshua N. Goldstein, MD, PhD[6], M. Edip Gurol, MD, MSc[5], Anand Viswanathan, MD, PhD[5], Steven Greenberg, MD, PhD[5], Alessandro Biffi, MD[4,5], Jonathan Rosand, MD, MSc[1,4], Christopher D. Anderson, MD, MMSc[1,2]. [1]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA, [2]Broad Institute, Cambridge, MA, USA, [3]Department of Medicine, Queen Mary Hospital, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong, [4]Henry and Allison McCance Center for Brain Health, Massachusetts General Hospital, Boston, MA, USA, [5]Department of Neurology, Massachusetts General Hospital, Boston, MA, USA, [6]Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA.*

129. Leber's Hereditary Optic Neuropathy (LHON)-Like Syndrome in Heteroplasmic Mitochondrial Mutations

Jane W. Chan, MD*, Alfredo A. Sadun, MD, PhD. Doheny Eye Center/ UCLA, Pasadena, CA, USA.*

130. Investigation of *RFC1* Expansions in Sporadic ALS

Ramita Dewan, MD[1]*, Bryan J. Traynor, MD, PhD[1], Henry Houlden, PhD[2], Andrea Cortese, MD[3], Luigi Ferrucci, MD, PhD[4], Susan Resnick, PhD[4], Yevgenya Abramzon, BS[1]. [1]Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD, USA, [2]Sobell Department of Motor Neuroscience and Movement Disorders, University College London, London, United Kingdom, [3]Sobell Department of Motor Neuroscience and Movement Disorders, University College London, Institute of Neurology, London, United Kingdom, [4]NIA, NIH, Baltimore, MD, USA.*

131. Rapid-Onset Dystonia Parkinsonism: Evolution of Clinical Phenotype 26 Years Post Diagnosis

Tarek Ali, MBBS, M.Ed, *Zain Guduru, MD. University of Kentucky, Lexington, KY, USA.*

132. Familial Creutzfeldt Jakob Disease: Uncommon & Under-Recognized

Venkataditya Dugyala, MD, *Maria Shoaib, MD, Ahmad A. Al Awwad, MD. Department of Neurology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.*

133. Age-at-Onset and Time-to-Event of Core Features in CLN3 (Batten) Disease

Margaux C. Masten, BA, *Jennifer Vermilion, MD, Heather R. Adams, PhD, Amy Vierhile, DNP, Frederick J. Marshall, MD, Christopher A. Beck, PhD, Erika F. Augustine, MD, Jonathan W. Mink, MD, PhD. University of Rochester, Rochester, NY, USA.*

134. Cross-Sectional and Longitudinal Natural History of CLN3 Disease Progression

Margaux C. Masten, BA, *Jennifer Vermilion, MD, Heather R. Adams, PhD, Amy Vierhile, DNP, Frederick J. Marshall, MD, Christopher A. Beck, PhD, Jonathan W. Mink, MD, PhD, Erika F. Augustine, MD. University of Rochester, Rochester, NY, USA.*

K-585. Genome-edited Human Hematopoietic Stem Cells Correct Lysosomal Storage Disorders

Edina Poletto, BS[1], Samantha G. Scharenberg, BS[2], Gurumurthy B. Channabasavaiah, PhD[3], Matthew Porteus, MD, PhD[2], ***Natalia Gomez-Ospina, MD, PhD[2]****. [1]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil, [2]Stanford University, Stanford, CA, USA, [3]University of Nebraska, Omaha, NE, USA.*

K-593. Infantile Spasms in CDKL5 Deficiency Disorder Respond Poorly to First Line Treatments

Heather Olson, MD, MS[1]*, Scott Demarest, MD[2], Elia Pestana-Knight, MD[3], Carolyn Daniels, BA[1], Caitlin Greene, BA[1], Michelle DeLeo, BA[1], Lindsay Swanson, MS[1], Jamie Love-Nichols, MS[1], Timothy Benke, MD, PhD[2], Chellamani Harini, MD[1], Annapurna Poduri, MD, MPH[1]. [1]Boston Children's Hospital, Boston, MA, USA, [2]Children's Hospital Colorado, Aurora, CO, USA, [3]Cleveland Clinic, Cleveland, OH, USA.*

K-594. Genetic Risk-Associations Causally Implicate Viral Response Pathways In Dementia With Tau Pathology

Jessica Rexach, MD PhD, *Damon Polioudakis, PhD, Timothy Chang, MD PhD, Daniel Geschwind, MD PhD. University of California Los Angeles, Los Angeles, CA, USA.*

Neuro-Ophthalmology

135. Neurosarcoidosis Related Vision Loss Mimicking Idiopathic Intracranial Hypertension

Margaret Lie, MA, *Gabriel Torrealba Acosta, MD, Alexandria Melendez-Zaidi, MD, Lydia Sharp, MD. Baylor College of Medicine, Houston, TX, USA.*

136. Retinal Amyloid Count as a Predictor of Hippocampal Volume and Cognitive Score: A Cohort Study

Tania Torbati, BSc[1,2]*, Oana M. Dumitrascu, MD[3], Patrick D. Lyden, MD[3], Ayesha Sherzai, MD[4], Dean Sherzai, MD, PhD[4], Dale Sherman, PhD[5], Julia Sheyn, BSc[1], Steven Verdooner, BSc[6], Keith L. Black, MD[1], Yosef Koronyo, MSc[1], Maya Koronyo-Hamaoui, PhD[1,7]. [1]Cedars-Sinai Medical Center, Department of Neurosurgery, Maxine Dunitz Neurosurgical Research Institute, Los Angeles, CA, USA, [2]Western University of Health Sciences, College of Osteopathic Medicine of the Pacific, Pomona, CA, USA, [3]Cedars-Sinai Medical Center, Department of Neurology, Los Angeles, CA, USA, [4]Loma Linda University, Department of Neurology, Loma Linda, CA, USA, [5]Cedars-Sinai Medical Center, Department of Neuropsychology, Los Angeles, CA, USA, [6]NeuroVision Imaging Inc., Sacramento, CA, USA, [7]Cedars-Sinai Medical Center, Department of Biomedical Sciences, Los Angeles, CA, USA.*

137. The Platysma in Hemifacial Spasm (HFS)

Frederick E. Lepore, MD*. Rutgers/Robert Wood Johnson Medical School, New Brunswick, NJ, USA.*

138. Interim Results of the MBCT-Vision Study Show Improvement of Visual Snow Syndrome (VSS) in the First Treatment Trial for VSS

Sui Hsien Wong, MD FRCP[1]*, Janet Wingrove, PhD CPsychol AFBPsS[2], Alistair Duncan, PhD[1]. [1]Guys and St Thomas' NHS Foundation Trust, London, United Kingdom, [2]South London and Maudsley NHS Foundation Trust, London, United Kingdom.*

Regenerative Medicine

139. New Ferritin-Based Tissue-Specific Genetic Vectors for MR Visualization of Neurogenesis

Anna Pishchelko, PhD[1], Anna Naumova, PhD[2], Veronique Daniëls, PhD[3], Irina Thiry, PhD[3], Mikhail Svetlik, PhD[1], Nikolay Nemirovich-Danchenko, PhD[1], Yana Tyumentseva, M.D.[1], ***Marina Khodanovich, PhD[1]****. [1]Tomsk State University, Tomsk, Russian Federation, [2]University of Washington, Seattle, WA, USA, [3]Leuven Viral Vector Core, KU Leuven, Leuven, Belgium.*

140. m^{6}A Methylation Defect in Schwann Cells Impairs Myelination and Peripheral Nerve Regeneration

Anna E. Johnson, BS[1]*, Jessica Joseph, PhD[1], Jami Scheib, PhD[1], Ruifa Mi, MD PhD[1], Flavia Millesi, BSc[1,2], Thomas*

G. W. Harris, MBChB[1], Nicholas von Guionneau, MBBS[1], Matthew Wilcox, BSc[3,4], Feng Zhang, PhD[5], Guo-Li Ming, MD PhD[5], Sami Tuffaha, MD[1], Ahmet Hoke, MD PhD[1]. [1]Johns Hopkins School of Medicine, Baltimore, MD, USA, [2]Medical University of Vienna, Vienna, Austria, [3]Royal National Orthopaedic Hospital, London, United Kingdom, [4]UCL Center for Nerve Engineering, London, United Kingdom, [5]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.

K-584. Active Demethylation of Genes within Subventricular Zone Cells Following Perinatal Hypoxic-Ischemic Injury May Promote Neurogenesis

*Thomas J. Robinson, BS[1], Ji Young Park, BS[1], Kevin Silva, MS[1], Frances Northington, MD[1], Hongjun Song, PhD[2], **Ryan J. Felling, MD, PhD**[1]. [1]Johns Hopkins School of Medicine, Baltimore, MD, USA, [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.*

Monday Poster Presentations

Global Neurology

141. Machine Learning the Neurological Manifestations of Covid-19 from Literature

***Abhishek Dutta, PhD**. University of Connecticut, Storrs, CT, USA.*

142. Immune Reconstitution Inflammatory Syndrome (IRIS) in the Central Nervous System: Limitations for Diagnosis in Resource Limited Settings

***Allison Navis, MD**[1], Omar Siddiqi, MD[2,3], Lorraine Chisimba, MBChB[3], Stanley Zimba, MBChB MMed[3], Susan Morgello, MD[1], Gretchen L. Birbeck, MD, MPH[4,3]. [1]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]University of Zambia School of Medicine, Lusaka, Zambia, [4]University of Rochester, Rochester, NY, USA.*

143. Evaluating the Impact of Antiretroviral and Antiseizure Medication Interactions on ARV Effectiveness among Outpatient Clinic Attendees in Zambia

***Allison Navis, MD**[1], Ifunanya Dallah, BA[2], Charles Mabeta, n/a[3], Kalo Musukuma, BSc, MS[4], Brent A. Johnson, PhD[2], Izukanji Sikazwe, MBChB, MPH[5], David R. Bearden, MD, MSCE[2], Gretchen L. Birbeck, MD, MPH[6,3]. [1]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]University of Rochester School of Medicine, Rochester, NY, USA, [3]Chikankata Epilepsy Care Team, Mazabuka, Zambia, [4]University Teaching Hospital, Lusaka, Zambia, [5]Center for Infectious Disease Research in Zambia (CIDRZ), Lusaka, Zambia, [6]University of Rochester School of Medicine, New York, NY, USA.*

144. Prognostic Utility of Daily Changes in Glasgow Coma Scale and the Full Outline of Unresponsiveness Score Measurement in Patients with Metabolic Encephalopathy, Central Nervous System Infections and Stroke in Uganda

*Amir Abdallah, MBChB, MMed[1], Bart M. Demaerschalk, MD, MSc, FRCP(C)[1], Nan Zhang, MS[2], Richard Butterfield, III, MA[2], **Cumara B. O'Carroll, MD, MPH**[1]. [1]Mayo Clinic, Phoenix, AZ, USA, [2]Mayo Clinic, Scottsdale, AZ, USA.*

145. Where There is No Neurologist: Developing a Curriculum for a New Neurology Training Program in Zambia

***Deanna Saylor, MD, MHS**[1], Omar K. Siddiqi, MD, MPH[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Harvard Beth Israel Deaconess Medical Center, Boston, MA, USA.*

146. The Influence of Sex on the Management and Outcomes of Individuals with Acute Traumatic Spinal Cord Injury: A Series of Propensity-Score Matched Cohort Studies

***Julio C. Furlan, MD, LLB, MBA, PhD, MSc, FRCPC**[1], Tian Shen, MSc[2], B. Catharine Craven, BA, MD, FRCPC, MSc[1]. [1]KITE - Toronto Rehabilitation Institute, University Health Network; and University of Toronto, Toronto, ON, Canada, [2]Praxis Spinal Cord Institute, Vancouver, BC, Canada.*

147. Clinical and Microbiological Characteristics of Bacterial Meningitis in Adults

***Jun-Sang Sunwoo, MD, PhD**[1], Hye-Rim Shin, MD[2], Han Sang Lee, MD[1], Jangsup Moon, MD, PhD[1], Soon-Tae Lee, MD, PhD[1], Keun-Hwa Jung, MD, PhD[1], Kyung-Il Park, MD, Ph[1], Ki-Young Jung, MD, PhD[1], Manho Kim, MD, Ph[1], Sang Kun Lee, MD, PhD[1], Kon Chu, MD, PhD[1]. [1]Seoul National University Hospital, Seoul, Korea, Republic of, [2]Dankook University Hospital, Seoul, Korea, Republic of.*

148. Age-Adjusted Outcomes of COVID-19 Among Patients with Pre-Existing Cerebrovascular Disorders

***Urvish Patel, MBBS, MPH**[1,2], Preeti Malik, MD, MPH[2], Achint Patel, MD, MPH[2], Dhaivat Shah, MD, MSCR[2], Abhishek Lunagariya, MD, MHA[1], Vishal Jani, MD[1]. [1]Creighton University School of Medicine, Omaha, NE, USA, [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA.*

149. Prevalence of Epilepsy in Latin America and the Caribbean (LAC): A Systematic Review and Meta-Analysis

***Alba Navarro-Flores, Medical Student**[1,2], Oscar Rivera-Torrejón, Medical Student[3,2], Andrely Huerta-Rosario, Medical Student[1,2], Roberto A. Molina, Medical Student[1,2], Victor Velásquez-Rimachi, MD[4,2], Carlos Alva-Díaz, MD, MSc[5],*

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150. Predictors of Stroke Mortality in Zambia

***Aparna Nutakki, MD in Progress**[1], Mashina Chomba, MBChB[2], Lorraine Chishimba, MBChB[2], Moses Mataa, MBChB[2], Stanley Zimba, MBChB, MMed[2], Deanna Saylor, MD, MHS[3]. [1]Rush Medical College, Chicago, IL, USA, [2]University Teaching Hospital, Lusaka, Zambia, [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA.*

151. Inpatient Stroke Epidemiology in Zambia

***Aparna Nutakki, MD in Progress**[1], Mashina Chomba, MBChB[2], Lorraine Chishimba, MBChB[2], Stanley Zimba, MBChB, MMed[2], Deanna Saylor, MD, MHS[3]. [1]Rush Medical College, Chicago, IL, USA, [2]University Teaching Hospital, Lusaka, Zambia, [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA.*

152. A Super Smeller Who is Allergic to Chemical Smells-Multiple Chemical Sensitivity Induced Hyperosmia

***Keerthana Kadiri, Medical Student, Intern**[1], Alan Hirsch, MD, Neurology and Psychiatry[2]. [1]Kakatiya Medical College, MGM Hospital, Warangal, Telangana, India, [2]Smell and Taste Treatment and Research Foundation, Chicago, IL, USA.*

153. Lateral Modified Brandt-Daroff Exercises (LMBDE): Introduction of a New Lateral Canal Benign Paroxysmal Positional Vertigo (BPPV) Treatment Maneuver Based on Simulation with a Biomechanical Model

*Michael Teixido, MD[1,2], Ryan Casserly, MD[1], **Lauren E. Melley, BS**[3]. [1]Christiana Care Health Systems, Newark, DE, USA, [2]Department of Otolaryngology, University of Pennsylvania, Philadelphia, PA, USA, [3]Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA.*

154. Neuroimaging in Zambian Children with HIV and New Onset Seizure: Findings from the CHASE Study

***Samuel Kampondeni, MMed**[1,2], Michael J. Potchen, MD[1,3], Izukanji Sikazwe, MBChB, MPH[4], Manoj Mathews, MMed[5], Musaku Mwenechanya, MMed[5], Colleen Hammond, AS[6], Ifunanya Dallah, BA[1], David Bearden, MD[1], Harris Gelbard, MD, PhD[1], Christopher Bositis, MD[7], Jason Okulicz, MD[8], Brent Johnson, PhD[1], Igor Koralnik, MD[9], Omar Siddiqi, MD, MPH[10], Melissa Elafros, MD, PhD[11], William Theodore, MD[12], Gretchen L. Birbeck, MD, MPH, DTMH[1,5]. [1]Univ of Rochester, Rochester, NY, USA, [2]Mpingwe Clinic, Limbe, Malawi, [3]Lusaka Apex Medical University, Lusaka, Zambia, [4]Center for Infectious Diseases Research in Zambia (CIDRZ), Lusaka, Zambia, [5]University Teaching Hospitals Children's Hospital, Lusaka, Zambia, [6]Michigan State University, East Lansing, MI, USA, [7]Greater Lawrence Family Health Center, Boston, MA, USA, [8]San Antonio Military Medical Center, San Antonio, TX, USA, [9]Northwestern University, Chicago, IL, USA, [10]Univ of Zambia, Lusaka, Zambia, [11]Johns Hopkins Univ, Baltimore, MD, USA, [12]Uniformed Services University, Bethesda, MD, USA.*

155. A Translational Medicine Approach for Clinical Trial Readiness of Min-102 (Leriglitazone) in Neurodegenerative and Neuroinflammatory Disorders

***Uwe Meya, MD**[1], Guillem Pina, -[1], Silvia Pascual, -[1], Marc Cerrada, PhD[1], Pilar Pizcueta, PhD[1], Marc Martinell, PhD[1], David Eckland, MD PhD[2], Jeroen van de Wetering, MD[3]. [1]Minoryx therapeutics, Mataro '(Barcelona), Spain, [2]Pharmaceutical Consultant, Watford, United Kingdom, [3]PRA Health Sciences, Groningen, Netherlands.*

156. Improvement of Cognitive Deficits and Neuronal Markers in HIV Associated Neurocognitive Disorder Mice Treated with Curcumin

***William Tyor, MD**[1], Rajeth Koneru, BS[1], Woldeab Haile, PhD[1], Aaron Scanlan, BS[2], Christina Gavegnano, PhD[2]. [1]Emory University School of Medicine and Atlanta VAMC, Atlanta, GA, USA, [2]Emory University School of Medicine, Atlanta, GA, USA.*

157. Variability of the Quantitative Neuroimaging Biomarkers

***Fatemeh Hajighasemi, MD**[1], Kamran Paynabar, PhD[2], Kourosh Jafari-Khouzani, PhD[3], Bruce Rosen, MD, PhD[1]. [1]Massachusetts General Hospital, Boston, MA, USA, [2]Georgia Institute of Technology, Atlanta, GA, USA, [3]IBM, Boston, MA, USA.*

158. Global Prevalence of Tuberculosis in the Central Nervous System: A Systematic Review and Meta-Analysis

*Jose Ernesto Fernández-Chinguel, Medical Student[1], Niels Pacheco-Barrios, Medical Student[2,3], Martina Guillermo-Roman, MD[4], Aaron Rodriguez Calienes, Medical Student[5], **Kevin Pacheco-Barrios, MD, MSc.**[6,7]. [1]Facultad de Medicina Humana, Universidad San Martín de Porres, Chiclayo, Peru, [2]Sociedad Científica de Estudiantes de Medicina Cayetano Heredia (SOCEMCH), Lima, Peru, [3]SYNAPSIS Mental Health and Neurology Non-Profit organization, Lima, Peru, [4]Facultad de Medicina, Universidad Nacional Mayor de San Marcos, Lima, Peru, [5]Facultad de Medicina Humana, Universidad San Martín de Porres, Lima, Peru, [6]Universidad San Ignacio de Loyola, Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Lima, Peru, [7]SYNAPSIS Mental Health and Neurology, Non-Profit Organization, Lima, Peru.*

159. Characterization of HIV-Associated Neurocognitive Impairment in Older Persons with HIV in Lima, Peru

Monica M. Diaz, M.D.[1,2], *Marcela Gil Zacarias, B.S.*[2], *Patricia Sotolongo, M.A.*[3], *Donald Franklin, Jr., B.S.*[1], *Mariana Cherner, Ph.D.*[1], *Serggio Lannata, M.D.*[4], *Ronald J. Ellis, M.D., Ph.D.*[1], *Patricia J. Garcia, M.D., Ph.D., M.P.H.*[2]. [1]*University of California, San Diego, San Diego, CA, USA,* [2]*Universidad Peruana Cayetano Heredia, Lima, Peru,* [3]*Alliant International University, San Diego, CA, USA,* [4]*Weill Institute for Neurosciences, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, USA.*

160. Improving Tuberculous Meningitis Diagnostics: A Combined Host and Pathogen Classifier

Prashanth S. Ramachandran, MBBS BMedSci[1], *Akshaya Ramesh, PhD*[1], *Fiona Creswell, MBBS*[2], *Carson Quinn, BS*[1], *Morris Rutakingirwa, MBBS*[3], *Ananta Bangdiwala, PhD*[4], *Enock Kagimu, MBBS*[3], *Kiiza Tadeo Kandole, MBBS*[3], *Lillian Tugume, MBBS*[3], *John Kasibante, MBBS*[3], *Kenneth Ssebambulidde, MBBS*[3], *Michael Okirwoth, MBBS*[3], *Abdu Musubire, MBBS*[3], *Charles Langelier, MD PhD*[5], *David Meya, MBBS*[3], *Emily Crawford, PhD*[5], *David Boulware, MD*[4], *Michael Wilson, MD MAS*[1]. [1]*Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA,* [2]*Clinical Research Department, London School of Hygiene and Tropical Medicine, London, United Kingdom,* [3]*Infectious Diseases Institute, Makerere University, Kampala, Uganda,* [4]*University of Minnesota, Minneapolis, MN, USA,* [5]*Chan Zuckerburg Biohub, San Francisco, CA, USA.*

161. Improving Neuromuscular Disease Clinical Care and Research in Zambia

Cleopatra Thurman, DO[1], *Alexander Carrese, DO*[1], *Michael Andary, MD*[1], *Michelle Kvalsund, DO/MS*[1], *Michael Horner, DO*[2]. [1]*Michigan State University, East Lansing, MI, USA,* [2]*Panorama Orthopedics and Spine Center, Denver, CO, USA.*

162. When to Test Primary Neurologic Patients for Covid-19 Infection

Gabriela Perez, DO[1], *Roberto Sanchez, MD*[1], *Ariol Labrada, MD*[1], *Ajay Banga, MS-III*[2], *Chassidy Teal, DO*[1]. [1]*Palmetto General Hospital, Hialeah, FL, USA,* [2]*Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Hialeah, FL, USA.*

163. Familial Influenza Associated Acute Necrotizing Encephalopathy

Qutub Khan, MD, ***Lei (Julie) Zhou, MD****, Donita Lightner, MD, Senna Munnikhuysen, MD. University of Kentucky, Lexington, KY, USA.*

164. Community Acquired Meningitis from Serratia Marcescens in an Adult: A Case Report

Mariyam Humayun, MBBS*, Shruti P. Agnihotri, MBBS. University of Alabama at Birmingham, Birmingham, AL, USA.*

165. Syphilitic Meningitis in Lusaka, Zambia

Mashina Chomba, MBChB[1,2], *Omar K. Siddiqi, MD, MPH*[1,3], *Sombo Fwoloshi, MBChB, MMed*[2], *Eugene Mubanga, MSc*[1], *Igor J. Koralnik, MD*[4], *Deanna Saylor, MD, MHS*[1,5]. [1]*University of Zambia - School of Medicine, Department of Internal Medicine, Lusaka, Zambia,* [2]*University Teaching Hospital, Department of Internal Medicine, Lusaka, Zambia,* [3]*Harvard Beth Israel Deaconess Medical Center, Department of Neurology, Boston, MA, USA,* [4]*Northwestern University Feinberg School of Medicine, Chicago, IL, USA,* [5]*John Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA.*

166. "Doctor Myself": Barriers to Effective Diagnosis and Treatment of Zambians with Meningitis

Melissa A. Elafros, MD PhD[1], *Chiti Bwalya, MPH*[2], *Godfrey Muchanga, BA*[3], *Mwangala Mwale, B.Ed.*[3], *Nachizya Namukanga, BA*[3], *Gretchen L. Birbeck, MD MPH DTMH*[4,5], *Mashina Chomba, MBChB*[6], *Achindike Mugala-Mulenga, MD*[6], *Michelle Kvalsund, DO MPH*[7,6], *Izukanji Sikazwe, MBChB MPH*[8], *Deanna Saylor, MD MPH*[1,6], *Peter Winch, MD MPH*[9]. [1]*Johns Hopkins University, Baltimore, MD, USA,* [2]*ZAMBART, Lusaka, Zambia,* [3]*The Meningitis Cascade of Care Study, Lusaka, Zambia,* [4]*University of Rochester, Rochester, NY, USA,* [5]*University Teaching Hospitals Children's Hospital, Lusaka, Zambia,* [6]*University of Zambia School of Medicine, Lusaka, Zambia,* [7]*Michigan State University, East Lansing, MI, USA,* [8]*CIDRZ, Lusaka, Zambia,* [9]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.*

167. Palliative Care Needs amongst Stroke Patients in Zambia

Moses Mataa, MBChB[1], *Aparna Nutakki, BS*[2], *Lorraine Chishimba, MBChB*[1], *Mashina Chomba, MBChB*[1], *Stanley Zimba, MBChB, MMed*[3], *Deanna Saylor, MD, MHS*[4]. [1]*University of Zambia School of Medicine, Lusaka, Zambia,* [2]*Rush University Medical Center, Chicago, IL, USA,* [3]*University Teaching Hospital, Lusaka, Zambia,* [4]*Johns Hopkins University School of Medicine, Baltimore, MD, USA.*

K-590. Folate Deficiency is Associated with Distal Symmetric Polyneuropathy in Zambian Clinics

Michelle Kvalsund, DO, MS[1,2], *Violet Kayamba, MBChB*[2], *Cleopatra Mwansa-Thurman, DO*[1], *Gretchen L. Birbeck, MD, MPH*[3,2], *David N. Hermann, MBBCh*[3]. [1]*Michigan State University, East Lansing, MI, USA,* [2]*University of Zambia, Lusaka, Zambia,* [3]*University of Rochester, Rochester, NY, USA.*

K-597. Elevations in Complement during S. Epidermidis Cerebrospinal Fluid Shunt Infection

Gwenn Skar[1], *Matthew Beaver, B.S.*[2], *Dragana Lugdzin, PhD*[2], *Ishwor Thapa, M.S.*[3], *Hesham Ali, PhD*[3], *Jessica Snowden, M.D.*[4], *Tammy Kielian, PhD*[2]. [1]*University of Nebraska,* [2]*University of Nebraska Medical Center, Omaha, NE, USA,* [3]*University of Nebraska Omaha, Omaha, NE, USA,*

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Multiple Sclerosis

168. The Power of Single Cell Technologies; from T Cell Receptor to Antigen(s) in Multiple Sclerosis

Naresha Saligrama, PhD[1], Ricardo A. Fernandes, PhD[2], Joy Pai, BS[2], Jorge Oksenberg, Phd[3], Ansuman Satpathy, Phd[2], Mark M. Davis, Phd[2]. [1]Washington University in St Louis, St Louis, MO, USA, [2]Stanford University, Stanford, CA, USA, [3]UCSF Weill Institute for Neurosciences, San Francisco, CA, USA.

169. Evaluating the Relative Contributions of Various Domains on Fall Rates Cross-Sectionally and Longitudinally in Persons with Multiple Sclerosis

Charles Van Liew, MA, MA, GCAS, CSCS[1], Jessie M. Huisinga, PhD[2], Daniel S. Peterson, PhD[1,3]. [1]Arizona State University, Phoenix, AZ, USA, [2]University of Kansas, Kansas City, KS, USA, [3]Phoenix VA Veterans Affairs Medical Center, Phoenix, AZ, USA.

170. Vestibular Function and Fatigue in People with Multiple Sclerosis

Graham D. Cochrane, Bachelor of Arts, Robert Motl, PhD, Jennifer B. Christy, PT, PhD, Khurram Bashir, MD. University of Alabama at Birmingham, Birmingham, AL, USA.

171. Continued Increase of Multiple Sclerosis and Neuromyelitis Optica in Japan: Updates from the 5th Nationwide Survey

Jun-ichi Kira, MD, PhD[1,2], Noriko Isobe, MD, PhD[1], Masaaki Niino, MD, PhD[3], Takuya Matsushita, MD,PhD[1], Yuri Nakamura, MD, PhD[2,4], Ichiro Nakashima, MD, PhD[5], Mitsuru Watanabe, MD, PhD[1], Yasunari Sakai, MD, PhD[6], Ayako Sakoda, MD, PhD[4], Jin Nakahara, MD, PhD[7], Izumi Kawachi, MD, PhD[8], Hirofumi Ochi, MD,PhD[9], Yuji Nakatsuji, MD, PhD[10], Yusei Miyazaki, MD, PhD[11], Juichi Fujimori, MD, PhD[5], Kenji Kufukihara, MD, PhD[7], Tatsusada Okuno, MD, PhD[12], Shoko Fukumoto, MD[1], Fumie Hayashi, MD[1], Kousuke Yonemoto, MD[6], Ryoji Taira, MD[6], Yoshikazu Nakamura, MD, MPH[13], Koshi Nakamura, MD, PhD[14], Kiyomi Sakata, MD, PhD, MPH[15], Rinako Shimada, DipHE[1], Makoto Matsui, MD, PhD[16]. [1]Department of Neurology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [2]Translational Neuroscience Center, Graduate School of Medicine, and School of Pharmacy at Fukuoka, International University of Health and Welfare, Okawa, Japan, [3]Department of Clinical Research, Hokkaido Medical Center, Sapporo, Japan, [4]Department of Neurology, Brain and Nerve Center, Fukuoka Central Hospital, International University of Health and Welfare, Fukuoka, Japan, [5]Department of Neurology, Tohoku Medical and Pharmaceutical University, Sendai, Japan, [6]Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [7]Department of Neurology, Keio University School of Medicine, Tokyo, Japan, [8]Department of Neurology, Niigata University, Niigata city, Japan, [9]Department of Neurology, Graduate School of Medicine, Ehime University, Toon, Japan, [10]Department of Neurology, Toyama University Hospital, Toyama, Japan, [11]Department of Neurology, Hokkaido Medical Center, Sapporo, Japan, [12]Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan, [13]Department of Public Health, Jichi Medical University, Shimotsuke, Japan, [14]Department of Public Health and Hygiene, University of the Ryukyus, Nakagami-gun, Japan, [15]Department of Hygiene & Preventive Medicine, Iwate Medical University, Shiwa-gun, Japan, [16]Department of Neurology, Kanazawa Medical University, Kahoku-gun, Japan.

172. Vascular Comorbidity is Associated with Lower Brain Volumes in a Large Multiple Sclerosis Cohort

Kathryn Fitzgerald, ScD[1], Anne Damian, MD[1], Devon Conway, MD[2], Ellen Mowry, MD, MCR[1]. [1]Johns Hopkins School of Medicine, Baltimore, MD, USA, [2]Mellen Center for Multiple Sclerosis at Cleveland Clinic, Cleveland, OH, USA.

173. Selective Ageusia in Multiple Sclerosis: Tasting Celery but Not the Dip

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174. Ablution Responsive Palinosmia in Multiple Sclerosis

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175. Leveraging COViMS Registry to Understand the Impact of COVID-19 on Multiple Sclerosis

Scott D. Newsome, DO[1], Robert J. Fox, MD[2], Gary R. Cutter, PhD[3], Bruce Bebo, PhD[4], Kathleen Costello, MS, ANP-BC[4], Pamela Kanellis, PhD[5], June Halper, MSN, APN-C[6], David K.B. Li, MD[7], Kottil W. Rammohan, MD[8], Anne H. Cross, MD[9], Amber Salter, PhD[10]. [1]Johns Hopkins School of Medicine, Baltimore, MD, USA, [2]Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland, OH, USA, [3]University of Alabama, Birmingham, AL, USA, [4]National Multiple Sclerosis Society, New York, NY, USA, [5]Multiple Sclerosis Society of Canada, Toronto, ON, Canada, [6]Consortium of Multiple Sclerosis Centers, Hackensack, NJ, USA, [7]University of British Columbia, Vancouver, BC, Canada, [8]University of Miami, Miami, FL, USA, [9]-Washington University School of Medicine, St. Louis, MO, USA, [10]Washington University, St. Louis, MO, USA.

176. Vascular Disease Risk Factors in Multiple Sclerosis (MS) is Associated with Brain Adenosine Triphosphate Abnormalities: Dysmetabolism May Drive MS Disease Progression

Vijayshree Yadav, MD, MCR[1], *Michael Lane, MD*[1], *Allison Fryman, MPH*[1], *Frank Bittner, DO*[1], *Valerie Anderson, PhD*[2], *Manoj Sammi, PhD*[2], *William Rooney, PhD*[2]. [1]*Oregon Health Science University and Department of Veterans Affairs MS Center of Excellence-West, Portland, OR, USA,* [2]*Oregon Health Science University, Portland, OR, USA.*

177. Progressive Multifocal Leukoencephalopathy Lesion and Brain Parenchymal Segmentation from MRI Using Serial Deep Convolutional Neural Networks

Omar Al-Louzi, MD[1,2], *Snehashis Roy, PhD*[3], *Ikesinachi Osuorah, B.S.*[2], *Prasanna Parvathaneni, PhD*[1], *Bryan Smith, MD*[4], *Joan Ohayon, M.S.N.*[2], *Pascal Sati, PhD*[1], *Dzung L. Pham, PhD*[5], *Steven Jacobson, PhD*[6], *Avindra Nath, MD*[4], *Daniel S. Reich, MD, PhD*[1], *Irene Cortese, MD*[2]. [1]*Translational Neuroradiology Section, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA,* [2]*Neuroimmunology Clinic, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA,* [3]*Section of Neural Function, National Institute of Mental Health, Bethesda, MD, USA,* [4]*Section of Infections of the Nervous System, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA,* [5]*Center for Neuroscience and Regenerative Medicine, The Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA,* [6]*Viral Immunology Section, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA.*

178. Brain Functional Connectivity is Related to Leptomeningeal Enhancement in Relapsing-Remitting Multiple Sclerosis: A 7-T MRI Study

Shun Yao, MD., PhD[1,2], *Jonathan Zurawski, MD*[3], *Renxin Chu, PhD*[3], *Shahamat Tauhid, MD*[3], *Rohit Bakshi, MD*[3], *Yanmei Tie, PhD*[1]. [1]*Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA,* [2]*Center for Pituitary Tumor Surgery, Department of Neurosurgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China,* [3]*Departments of Neurology, Laboratory for Neuroimaging Research, Partners MS Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.*

179. Delayed-Onset Demyelinating Lesions after Radiation Injury: A MS Mimic

Sofia Raefsky, MS3, ***Amit Chaudhari, MD PhD****, Michael Y. Sy, MD PhD. University of California Irvine, Anaheim, CA, USA.*

180. Tumefactive Multiple Sclerosis (TMS): A Case Series of This Uncommon Yet Challenging Variant of MS

Bhanu Gogia, MD*, Neeharika Thothempudi, MD, Maria Abraham, B.S., Joseph V. Villareal, B.S., Joanne Allieza G. Acevedo, B.S.; MD, Xiang Fang, MD. University of Texas Medical Branch, Galveston, TX, USA.*

181. Radiologically Isolated Syndrome vs. Multiple Sclerosis; Case Report with Review of the Literature

Christopher Smith, MD*, Nicholas Helmstetter, MD, Michael Soliman, MD, Jesus Lovera, MD. LSU HSC, New Orleans, LA, USA.*

K-591. Preferential Correlations between Thalamic Subregions and Neuroperformance Measures in Progressive Multiple Sclerosis.

Kedar Mahajan, MD, PhD*, Kunio Nakamura, PhD, Robert Fox, MD, Daniel D. Ontaneda, MD, MSc. Cleveland Clinic, Cleveland, OH, USA.*

Behavioral Neurology

182. Effects of Methylphenidate on Verbal Creativity, Verbal Fluency, and Convergent Thinking Tasks in Adults with Attention-Deficit Hyperactivity Disorder

Bradley J. Ferguson, PhD[1], *Alyssia A. Gonzalez, (none)*[2], *Andrea Scheaffer, BS*[1], *Molly McBride, BS*[1], *David C. Wang, BS*[3], *Eric S. Hart, PhD*[1], *David Q. Beversdorf, MA*[1]. [1]*University of Missouri, Columbia, MO, USA,* [2]*California State University San Marcos, San Marcos, CA, USA,* [3]*Emory University, Atlanta, GA, USA.*

183. Cognitive Impairment and Risk Factors of LATE, a Novel Degenerative Pathology

S. Ahmad Sajjadi, MD, PhD*, Michael Phelan, PhD, Rui Yan, BS, Chu-Ching Ho, BS, Kiana Scambray, BS, Davis Woodworth, PhD, Maria Corrada, ScD, Claudia Kawas, MD. University of California, Irvine, Irvine, CA, USA.*

184. Do Children with Weakness in Grammar Understanding Have Only Language Deficit?

Sergey Kiselev, Ph.D. *Ural Federal University, Ekaterinburg, Russian Federation.*

185. Weakness in Visuospatial Abilities in Children Can Be Caused by Computer Game Addiction

Sergey Kiselev, Ph.D. *Ural Federal University, Ekaterinburg, Russian Federation.*

186. Can the Maternal Mindfulness Training during Pregnancy Influence Neurocognitive Development of Offspring?

Sergey Kiselev, Ph.D. *Ural Federal University, Ekaterinburg, Russian Federation.*

187. Children with Attention Deficit Hyperactivity Disorder Benefit from Yoga Training

Sergey Kiselev, Ph.D. *Ural Federal University, Ekaterinburg, Russian Federation.*

188. Post-Stroke Deficit Prediction from Lesion and Indirect Structural and Functional Disconnection

Alessandro Salvalaggio, MD[1]*, Michele De Filippo De Grazia, PhD*[2]*, Marco Zorzi, PhD*[3]*, Michel Thiebaut De Schotten, PhD*[4]*, Maurizio Corbetta, MD PhD*[5,6]*.* [1]*Padova Neuroscience Center, Department of Neuroscience,Univeristy of Padova, Padova, Italy,* [2]*IRCCS San Camillo Hospital, Venice, Italy,* [3]*Department of General Psychology, and Padova Neuroscience Center (PNC), University of Padova, Padova, Italy,* [4]*Brain Connectivity and Behaviour Laboratory, Sorbonne Universities, Paris, France,* [5]*Clinica Neurologica, Department of Neuroscience, and Padova Neuroscience Center (PNC), University of Padova, Padova, Italy,* [6]*Department of Neurology, Radiology, Neuroscience Washington University School of Medicine, St. Louis, MO, USA.*

189. Autopsy Correlations of Flortaucipir and Pittsburgh Compound B Pet in Frontotemporal Lobar Degeneration

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190. "Where Did the Groceries Come From?": A Case of Acute Amnestic Syndrome

Andrew Van Velsor, B.S.*, Prashant A. Natteru, MD, Silu Lu, MD, Shreyas Gangadhara, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

191. The Impact of Diet and Nutrients on Episodic Memory across the Adult Lifespan: A Systematic Review and Meta-Analysis

Kyoungeun Lee, MS*, Audrey Duarte, Ph.D. Georgia Institute of Technology, Atlanta, GA, USA.*

192. Lizard Skin Replaces Pig Skin: Cotard's Syndrome with Zoanthropy in a Football Player Due to Presumed Chronic Traumatic Encephalopathy

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193. Neurogenic Maturational Correlates of the Anxiolytic Effect of Fluoxetine in Macaques

Eric M. Schoenfeld, BA[1]*, Mohamed Elsayed, MBBCh*[2]*, Jeremy D. Coplan, MD*[2]*.* [1]*SUNY Downstate College of Medicine, Brooklyn, NY, USA,* [2]*SUNY Downstate Department of Psychiatry & Behavioral Sciences, Brooklyn, NY, USA.*

194. Fire Induced Ageusia and Anosmia

Harsimran Bakhshi, Associate*. Windsor University School of Medicine, Brighton's Estate, Cayon, Saint Kitts and Nevis.*

195. Tabescent in Amyotrophic Lateral Sclerosis: Cacogeusia without Dysgeusia

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196. An Unusual Case of Stalking: The Neurologic Implications of Erotomania in Decompensated Schizoprenia

Jenny Abdulkarim, M.S.*, Khai Tran, M.D., Panagiota Korenis, M.D. BronxCare Health Systems, Bronx, NY, USA.*

197. Dissociable Systems for Recognizing Places and Navigating Through Them: Causal and Developmental Evidence

Stephanie Wahab, B.S.[1]*, Sama Radwan, B.S.*[2]*, Frederik Kamps, B.S., M.A.*[2]*, Daniel Dilks, PhD*[2]*.* [1]*Medical College of Georgia, Augusta, GA, USA,* [2]*Emory University, Atlanta, GA, USA.*

198. Haptic Training Enhances Visual Executive Attention

Yu Luo, BS[1]*, Jicong Zhang*, Ph.D.*[1]*, Chia-Chia Liu, Ph.D.*[2]*, Tao Liu, Ph.D.*[1]*.* [1]*Beihang University, Beijing, China,* [2]*University of Virginia School of Medicine, Virginia, VA, USA.*

199. Enhancing Frontal Dopamine Tone Improves Working Memory Maintenance

Andrew Kayser, M.D., Ph.D.[1]*, Daniella Furman, Ph.D.*[1]*, Zhihao Zhang, Ph.D.*[2]*, Christopher Chatham, Ph.D.*[3]*, Maxwell Good, B.A.*[2]*, David Badre, Ph.D.*[4]*, Ming Hsu, Ph.D.*[2]*.* [1]*University of California at San Francisco, San Francisco, CA, USA,* [2]*University of California at Berkeley, Berkeley, CA, USA,* [3]*F. Hoffman La Roche AG, Geneva, Switzerland,* [4]*Brown University, Providence, RI, USA.*

200. Effects of Viral Load on Neuroimaging and Neuropsychological Performance in HIV-Positive Adults

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201. SSRIs May Mitigate the Relationships between Depression and Language Output and between Depression and Lesion Volume after Stroke

***Colin M. Stein, B.A.**, Emily B. Goldberg, M.S., CCC-SLP, Delaney Ubellacker, B.A., Argye E. Hillis, M.D., M.A. Johns Hopkins School of Medicine, Baltimore, MD, USA.*

202. Weakness of Memory in Delayed Recall Condition is Specific Deficit in Children with ADHD

***Eleonora Mirzajonova, N/A**[1], Sergey Kiselev, Ph.D.[2]. [1]Fergana State University, Fergana, Uzbekistan, [2]Ural Federal University, Ekaterinburg, Russian Federation.*

203. A Case of Hallucinations and Palatal Myoclonus: Unraveling the Truth

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204. Eye Movements Abnormalities as Early Biomarker of Alzheimer's Disease: An Ecological Approach

***Andrea Zangrossi, Post-doc**, Giovanni Zorzi, PhD student, Annachiara Cagnin, Professor, Giulia Campana, Student, Lucrezia Bristot, Student, Maurizio Corbetta, Full Professor. University of Padua, Padua, Italy.*

205. Guideline for Repetitive Transcranial Magnetic Stimulation Treatment of Major Depressive Disorder Using Resting State Functional Magnetic Resonance Imaging

***Daniel Fino, MSc**[1,2], Roxana Galeno, MD[3,4], Sebastián G. Moguilner, PhD[5,6], Jorge Quiroga, Psy[3], Luciano A. Rivetti, MSc[5], María C. Huetagoyena, Psy[3,7], Federico J. González, MSc[5,6], Pedro P. Ariza, MD[1,5]. [1]Fundación Argentina para el Desarrollo en Salud, Mendoza, Argentina, [2]Universidad Nacional de Cuyo, Mendoza, Argentina, [3]Neuromed, Mendoza, Argentina, [4]Universidad Maza, Mendoza, Argentina, [5]Fundación Escuela de Medicina Nuclear, Mendoza, Argentina, [6]Comisión Nacional de Energía Atómica, Buenos Aires, Argentina, [7]Universidad del Aconcagua, Mendoza, Argentina.*

206. Lesion Network Mapping of Mania Symptoms Caused by Focal Brain Lesions

***Daniel Talmasov, MD**[1,2], Gonçalo Cotovio, MD[3], J. Bernardo Barahona-Corrêa, MD, PhD[3], Joey Hsu, BS[4], Suhan Senova, MD, PhD[3], Ricardo Ribeiro, MSC[3], Louis Soussand, MSc[4], Ana Velosa, MD[5], Vera Cruz e Silva, MD[5], Natalia Rost, MD[6], Ona Wu, PhD[7], Alexander L. Cohen, MD, PhD[8], Albino J. Oliveira-Maia, MD, MPH, PhD[3], Michael D. Fox, MD, PhD[4]. [1]-New York University School of Medicine, New York, NY, USA, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [3]Champalimaud Research and Clinical Centre, Lisbon, Portugal, [4]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA, [5]Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal, [6]Massachusets General Hospital, Harvard Medical School, New York, NY, USA, [7]Massachusetts General Hospital, Boston, MA, USA, [8]Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.*

207. Unveiling the Presence and Nature of Auditory Comprehension Deficits in Primary Progressive Aphasia

***Jonanthan Sikora, BS**[1], Colin M. Stein, BA[2], Delaney Ubellacker, BA[2], Alexandra Walker, BA[2], Donna C. Tippett, MPH, MA, CCC-SLP[3]. [1]Department of Neurology Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Department of Neurology Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]Departments of Neurology, Otolaryngology-Head and Neck Surgery, Physical Medicine and Rehabilitation Johns Hopkins University School of Medicine, Baltimore, MD, USA.*

K-595. Fetal Brain Development In Congenital Heart Disease

***Caitlin K. Rollins, MD**[1,2], Cynthia M. Ortinau, MD[3], Valerie Rofeberg, M.S.[1], Kevin G. Friedman, MD[1,2], Maggie Mittleman, B.A.[1], Ali Gholipour, PhD[1,4], David Wypij, PhD[1,5], Simon K. Warfield, PhD[1,2], Jane W. Newburger, MD, MPH[1,2]. [1]Boston Children's Hospital, Boston, MA, USA, [2]Harvard Medical School, Boston, MA, USA, [3]Washington University in St. Louis, St. Louis, MO, USA, [4]Harvard Medical SChool, Boston, MA, USA, [5]Harvard TH Chan School of Public Health, Boston, MA, USA.*

Headache and Pain

208. Increased Headache Prevalence in Patients with Chronic Neuropathic Pain

***Hsinlin Thomas Cheng, MD, PhD**, Vi Le, BS, Jennifer Cheng, MPH, NP. Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA.*

209. Utilizing Telemedicine in an Interdisciplinary Academic Headache Center

***Sandhya Ravikumar, MD**, Susan Axtell, Psy.D., Malia Sako, OTD, OTR/L, Lori Ginoza, PT, DPT. University of Southern California, Los Angeles, CA, USA.*

210. Triggers of Status Migrainosus and Higher Morbidity Amongst Migraineurs

Urvish K. Patel, MBBS, MPH[1], *Dhaivat Shah, MD, MSCR*[1], *Preeti Malik, MD, MPH*[1], *Salma Yousuf, MBBS*[1], *Aisha Ashraf, MBBS*[1], *Gaurav Tyagi, DDS*[2], *Kogulavadanan Arumaithurai, MD*[3], *Ashish Kapoor, MD*[4], *Tapan Kavi, MD*[5]. [1]*Icahn School of Medicine at Mount Sinai, New York, NY, USA,* [2]*Rutgers School of Dental Medicine, Newark, NJ, USA,* [3]*Mayo Clinic Health System, Albert Lea, MN, USA,* [4]*Jersey City Medical Center, RWJ Barnabas Health/Bayonne Medical Center, CarePoint Health, Bayonne, NJ, USA,* [5]*Cooper Medical School of Rowan University, Camden, NJ, USA.*

211. CGRP Monoclonal Antibodies: Targeted Migraine Treatment and Cardiovascular Safety Profile

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212. Distinct Clinical Features of Red Ear Syndrome in Pediatric Population

Kyle C. Tsai, none[1], *Laura J. Wu, MD*[2]. [1]*Michael E. DeBakey High School for Health Professions, Houston, TX, USA,* [2]*UTMB, Galveston, TX, USA.*

213. Case Report: Transient Global Amnesia in a Child

Nina Navalkar, B.S.[1], *Anuradha Pavuluri, M.D.*[2], *Joseph Trasmonte, M.D.*[3]. [1]*Mercer University School of Medicine, M.D. Program, Macon, GA, USA,* [2]*Department of Pediatrics, Beverly Knight Olson Children's Hospital, Navicent Health, Macon, GA, USA,* [3]*Department of Pediatrics, Beverly Knight Olson Children's Hospital, Navicent Health, Macon, GA, USA.*

214. Outcomes of Patients Presenting with Headaches Hospitalized with COVID-19

Suraj K. Jaladanki, BS[1,2], *Arvind Kumar, BS*[1,2], *Tielman Van Vleck, PhD*[1,2], *Sulaiman Somani, BS*[1,2], *Shan Zhao, MD, PhD*[1,2], *Girish N. Nadkarni, MD, MPH*[1,2], *Alexander Charney, MD, PhD*[1,2]. [1]*Icahn School of Medicine at Mount Sinai, New York, NY, USA,* [2]*The Mount Sinai COVID Informatics Center, New York, NY, USA.*

215. Efficacy and Safety of AXS-07 (MoSEIC™ Meloxicam/Rizatriptan) in the Acute Treatment of Migraine: Results from the INTERCEPT Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial

Amanda Jones, PharmD[1], *Cedric O'Gorman, MD*[1], *Stewart J. Tepper, MD*[2], *Richard B. Lipton, MD*[3], *Herriot Tabuteau, MD*[1]. [1]*Axsome Therapeutics, New York, NY, USA,* [2]*Geisel School of Medicine at Dartmouth, Hanover, NH, USA,* [3]*Albert Einstein College of Medicine, Bronx, NY, USA.*

216. Migraine and Functional Impairment Associated with Driving: Results of the OVERCOME Study

Bert Vargas, MD[1], *Hu Li, MD, PhD*[1], *Andre Araujo, PhD*[1], *Dawn Buse, PhD*[2], *Erin Gautier Doty, MD*[1], *Yongin Kim, MSc*[1], *Richard Lipton, MD*[1], *Li Loo, MD*[1], *Robert Nicholson, PhD, FAHS*[1], *Eric Pearlman, USDM CGRP*[1], *Michael Reed, Dr*[1], *Robert Shapiro, MD, PhD*[3], *Anthony Zagar, PhD*[1]. [1]*Eli Lilly and Company, Indianapolis, IN, USA,* [2]*Albert Einstein College of Medicine, New York City, NY, USA,* [3]*University of Vermont Medical Center, Indianapolis, VT, USA.*

217. Stigmatizing Attitudes Towards People with Migraine by People without Migraine: Results of the Overcome Study (2017-6229-005)

Bert Brandon Vargas, MD. *Eli Lilly and Company, Indianapolis, IN, USA.*

218. A Close Association of Pain Freedom with Freedom from Most Bothersome Symptom and from Migraine-Related Functional Disability in Lasmiditan Studies Samurai and Spartan

Bert Brandon Vargas, MD[1], *Simin K. Baygani, PhD*[1], *Paula Hauck, PhD*[1], *John Krege, MD*[1], *Richard Lipton, MD*[1], *Li Loo, MD*[1], *Eric Pearlman, MD*[1], *Stewart J. Tepper, MD*[2], *Raghavendra Vasudeva, PhD*[1]. [1]*Eli Lilly and Company, Indianapolis, IN, USA,* [2]*Dartmouth University, Hanover, NH, USA.*

219. Efficacy and Safety of AXS-07 (MoSEIC™ Meloxicam/Rizatriptan) in the Acute Treatment of Migraine: Results from the MOMENTUM Phase 3, Randomized, Double-Blind, Active- and Placebo-Controlled Trial

Cedric O'Gorman, MD[1], *Amanda Jones, PharmD*[1], *Richard B. Lipton, MD*[2], *Stewart J. Tepper, MD*[3], *Herriot Tabuteau, MD*[1]. [1]*Axsome Therapeutics, New York, NY, USA,* [2]*Albert Einstein College of Medicine, Bronx, NY, USA,* [3]*Geisel School of Medicine at Dartmouth, Hanover, NH, USA.*

220. Efficacy of Galcanezumab in Patients Who Had Not Benefited From Commonly Prescribed Migraine Preventive Treatments

Dulanji Kuruppu, MD. *Eli Lilly and Company, Indianapolis, IN, USA.*

221. Adverse Event Profiles of Therapies That Target the Calcitonin Gene-Related Peptide (CGRP) Pathway, During the First Six Months after Launch: A Real-World Data Analysis Using the FDA Adverse Events Reporting System (FAERS)

Stephen D. Silberstein, MD[1], *Shoshana Reshef, PhD*[2], ***Joshua M. Cohen, MD, MPH, FAHS***[2], *Sanjay Gandhi, PhD*[2], *Michael Seminerio, PhD*[2], *Verena Ramirez Campos, MD*[2], *Yoel Kessler, MD*[2], *Stephen F. Thompson, PhD*[2], *Andrew*

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222. Narrative Review of Risk Factors and the Burden of Medication Overuse Headache on Quality-of-Life, Disability Outcomes, and Comorbidities

*Christian Lampl, MD[1], **Joshua M. Cohen, MD, MPH, FAHS**[2], Stephen F. Thompson, PhD[2], Krishna Tangirala, PhD[2], Andrew H. Ahn, MD[2], Verena Ramirez Campos, MD[2], Ravi Iyer, PhD, MBA[2]. [1]Headache Medical Centre, Linz, Austria, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA.*

223. Efficacy of Fremanezumab in Subjects with Migraine and Prior Inadequate Response to Valproic Acid, Topiramate, or Onabotulinumtoxina in the Open-Label Period of the International, Multicenter, Randomized, Placebo-Controlled FOCUS Study

*Abraham J. Nagy, MD[1], Xiaoping Ning, MD[2], Maja Galic, PhD[3], **Joshua M. Cohen, MD, MPH, FAHS**[2], Ronghua Yang, PhD[2], Michael Seminerio, PhD[2], Laszlo Mechtler, MD[4]. [1]Nevada Headache Institute, Las Vegas, NV, USA, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA, [3]Teva Pharmaceuticals, Amsterdam, Netherlands, [4]Dent Neurologic Institute, Amherst, NY, USA.*

224. Long-Term Efficacy of Fremanezumab in Patients with Episodic Migraine and Chronic Migraine Who Failed at Least One Prior Migraine Preventive Medication: Results from 6- and 12-Month Studies

*Carrie Dougherty, MD[1], Xiaoping Ning, MD[2], **Joshua M. Cohen, MD, MPH, FAHS**[2], Ronghua Yang, PhD[2], Verena Ramirez Campos, MD[2], Michael Seminerio, PhD[2], Stephen D. Silberstein, MD[3]. [1]Department of Neurology, MedStar Georgetown University Hospital, Washington, D.C., Washington, DC, USA, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA, [3]Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA.*

225. Pooled Analysis of Safety and Tolerability with Fremanezumab Treatment in Patients with Migraine and Baseline Cardiovascular Medication or Concomitant Triptan Use

*Gianluca Coppola, MD, PhD[1], Xiaoping Ning, MD[2], Yoel Kessler, MD[2], **Joshua M. Cohen, MD, MPH, FAHS**[2], Evelyn Du, MD[2], Piero Barbanti, MD, PhD[3]. [1]Sapienza University of Rome Polo Pontino, Department of Medico-Surgical Sciences and Biotechnologies, Rome, Italy, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA, [3]Headache and Pain Unit, IRCCS San Raffaele Pisana, Rome, Italy.*

226. Efficacy of Fremanezumab in Patients with Migraine and Documented Inadequate Response to 3 or 4 Migraine Preventive Medication Classes and Medication Overuse in the International, Multicenter, Randomized, Placebo-Controlled FOCUS Study

*Ladislav Pazdera, MD[1], Xiaoping Ning, MD[2], Verena Ramirez Campos, MD[2], Ronghua Yang, PhD[2], **Karen Carr, MD**[2], Joshua M. Cohen, MD, MPH, FAHS[2]. [1]Vestra Clinics, Rychnov nad Kněžnou, Czech Republic, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA.*

227. Depression and Migraine - A Double Whammy on Patient-Reported Health

*Zubair Ahmed, MD[1], Ryan Honomichl, MS[1], Stephen F. Thompson, PhD[2], Joshua M. Cohen, MD, MPH, FAHS[2], Andrew Schuster, BA[1], Nicolas R. Thompson, MS[1], Brittany Lapin, PhD[1], Belinda Udeh, PhD[1], Verena Ramirez Campos, MD[2], **Lynda J. Krasenbaum, MSN, ANP-BC**[2], Irene L. Katzan, MD[1]. [1]Cleveland Clinic, Cleveland, OH, USA, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA.*

228. A Real-World Perspective on the Characteristics of Migraine Patients Prescribed Ajovy, Emgality, or Aimovig in the United States

*Joshua M. Cohen, MD, MPH, FAHS[1], Shivani Pandya, MS[2], **Lynda J. Krasenbaum, MSN, ANP-BC**[1], Stephen F. Thompson, PhD[1], Chien-Cheng Chen, MS, PhD[2], Krishna Tangirala, PhD[1]. [1]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA, [2]STATinMED Research, Plano, TX, USA.*

229. Changing Perceptions of Interdisciplinary Care for Headache Patients via Telehealth during Covid Pandemic

***Soma Sahai-Srivastava, MD**, Lori Ginoza, NA, Lindsey Reeves, NA, Malia Sako, NA, Melina Allahverdian, NA, Sandhya Ravikumar, NA, Paul Henri Cesar, NA, Lauren Green, NA. USC Keck School of Medicine, Los Angeles, CA, USA.*

230. Efficacy of Fremanezumab in Migraine Patients with Medication Overuse and Documented Inadequate Response to 2-4 Migraine Preventive Medication Classes: Subgroup Analysis of the Randomized, Placebo-Controlled FOCUS Study

*Stephen Silberstein, MD[1], Joshua M. Cohen, MD[2], **Verena Ramirez Campos, MD**[2], Ronghua Yang, PhD[2], Maja Galic, PhD[3], Xiaoping Ning, MD[2], Adelene Jann, MD[4]. [1]Jefferson Headache Center, Philadelphia, PA, USA, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA,*

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231. Efficacy and Safety of Fremanezumab in Patients with Episodic and Chronic Migraine and Documented Inadequate Response to 2-4 Classes of Migraine Preventive Medications during the Open Label Period of the Phase 3b FOCUS Study

*Messoud Ashina, MD, PhD[1], Joshua M. Cohen, MD, MPH, FAHS[2], Maja Galic, PhD[3], **Verena Ramirez Campos, MD**[2], Ronghua Yang, PhD[2], Xiaoping Ning, MD[2], Hans-Christoph Diener, MD[4]. [1]Danish Headache Center, Department of Neurology, Rigshospitalet, Glostrup, Denmark, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA, [3]Teva Pharmaceuticals, Amsterdam, Netherlands, [4]Universitätsklinikum Essen, Essen, Germany.*

232. Safety and Tolerability of Fremanezumab in Patients with Episodic and Chronic Migraine: A Pooled Analysis of Phase 3 Studies

*Peter McAllister, MD[1], Xiaoping Ning, MD[2], Yoel Kessler, MD[2], Joshua M. Cohen, MD, MPH, FAHS[2], **Verena Ramirez Campos, MD**[2], Ronghua Yang, PhD[2]. [1]New England Center for Neurology and Headache, Stamford, CT, USA, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA.*

233. Pooled Analysis of Cardiovascular Safety with Fremanezumab Treatment in Patients with Migraine by Cardiovascular History and Number of Cardiovascular or Cerebrovascular Risk Factors

*Stephanie J. Nahas, MD[1], Tim P. Jürgens, MD[2], Yoel Kessler, MD[3], Xiaoping Ning, MD[3], Joshua M. Cohen, MD, MPH, FAHS[3], **Verena Ramirez Campos, MD**[3], Evelyn Du, MD[3], Stephen D. Silberstein, MD[1]. [1]Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA, [2]Dept. of Neurology, Headache Center North-East, University Medical Center of Rostock, Rostock, Germany, [3]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA.*

234. Efficacy with Fremanezumab in Migraine Patients with Comorbid Moderate to Severe Depression and Documented Inadequate Response to 2-4 Classes of Migraine Preventive Treatments: Subgroup Analysis of the Randomized, Placebo-Controlled FOCUS Study

*Richard B. Lipton, MD[1], Joshua M. Cohen, MD[2], **Verena Ramirez Campos, MD**[2], Ronghua Yang, PhD[2], Xiaoping Ning, MD[2], Maja Galic, MD[3], Dawn C. Buse, PhD[1]. [1]Department of Neurology, Albert Einstein College of Medicine, New York, NY, USA, [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA, USA, [3]Teva Pharmaceuticals, Amsterdam, Netherlands.*

235. Pneumocephalus: A Unique Complication of Mastoiditis and Cerebral Venous Sinus Thrombosis

***Aman Deep, MD**, Andrew N. Wilner, MD. University of Tennessee Health Science Center Neurology, Memphis, TN, USA.*

236. Alien Limb Can Be a Headache: A Rare Migraine Presentation

***Maria Shoaib, MD**, Syeda Dania Shujaat, MD, Ahmad A. Al Awwad, MD. Department of Neurology, University of Oklahoma Health Sciences Center., Oklahoma City, OK, USA.*

237. Self-Reported Ace Exposure in Adolescents Increases Odds of Frequent Headache: A Cross-Sectional Analysis

***Marissa M. Anto, MD, MSc**, Christina L. Szperka, MD, MSCE. The Children's Hospital of Philadelphia, Philadelphia, PA, USA.*

238. # Headache: When a Common Problem Becomes a Neurological Emergency in Acute Stroke Patients

***Patricia A. Olson, MD, PhD**, Jessica D. Lee, MD. University of Kentucky College of Medicine, Department of Neurology, Lexington, KY, USA.*

239. A Unique Case of Metal Allergy in an Occipital Nerve Stimulator Implant

***Tanvir Khosla, MD**[1], Nikhraj Brar, MD[2], Ramana Naidu, MD[3]. [1]GME Southern Hills Hospital, Las Vegas, NV, USA, [2]Providence Health, Mission Hills, CA, USA, [3]California Orthopedics & Spine, Larkspur, CA, USA.*

Pain Mechanisms & Treatment

240. Elevated Dietary Omega-6 Fatty Acids Exacerbate Mechanical and Cold Hypersensitivity in Diabetic Neuropathy

***Jacob T. Boyd, PhD**, Peter M. LoCoco, PhD, Kenneth M. Hargreaves, DDS, PhD. University of Texas Health - San Antonio, San Antonio, TX, USA.*

241. Improvement in Pain and Physical Function Following Subcutaneous Tanezumab Treatment in Patients with Osteoarthritis

*Asya Gutman, Doctor of Medicine[1], Erik Shaw, Doctor of Medicine[2], Yvonne D'Arcy, Nurse Practitioner[3], Evan F. Ekman, Doctor of Medicine[4], Jerry A. Hall, Doctor of Medicine[5], Leslie Tive, Doctor of Medicine[6], **David Semel, Doctor of Medicine**[6]. [1]New York Pain Relief Medicine, New York, NY, USA, [2]Shepherd Center, Atlanta, GA, USA, [3]Independent Nurse Practitioner, Vedra Beach, FL, USA, [4]Aiken Physicians Association, Aiken, SC, USA, [5]Eli Lilly & Company, Indianapolis, IN, USA, [6]Pfizer Inc., New York, NY, USA.*

242. Subcutaneous Tanezumab versus NSAID for the Treatment of Osteoarthritis: Neurological Safety in a Randomized, Double-Blind, Active-Controlled, 80-Week Phase 3 Study

*Paola Sandroni, Doctor of Medicine[1], Kenneth C. Gorson, Doctor of Medicine[2], Phillip A. Low, Doctor of Medicine[1], David J. Hunter, Doctor of Medicine[3], Glenn C. Pixton, PhD[4], Robert J. Fountaine, Doctor of Medicine[5], **Mark T. Brown, Doctor of Medicine**[5], Lars Viktrup, Doctor of Medicine[6], Christine West, Doctor of Medicine[7], Kenneth M. Verburg, Doctor of Medicine[5]. [1]Mayo Clinic, Rochester, MN, USA, [2]St. Elizabeth's Medical Center, Brighton, MA, USA, [3]Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia, [4]Pfizer Inc., Morrisville, NC, USA, [5]Pfizer Inc., Groton, CT, USA, [6]Eli Lilly & Company, Indianapolis, IN, USA, [7]Pfizer Inc., New York, NY, USA.*

243. Worldwide Frequency of Phantom Limb Pain in People with Amputations: A Systematic Review and Meta-Analysis

Kevin Pacheco-Barrios, MD, MSc.[1,2], *Damaris Ramirez-Alva, Medical Student*[3,4], *Ana Balbuena-Pareja, MD*[2], *Niels Pacheco-Barrios, Medical Student*[5,4], *Stefano Giannoni-Luza, MD*[2,4], *Anna Carolina Gianlorenço, PhD*[2], *Luna Vasconcelos Felippe, Medical Student*[2], *Ivan Chacha-Angulo, Medical Student*[3,4], *Felipe Fregni, MD, PhD*[2]. [1]*Universidad San Ignacio de Loyola, Vicerrectorado de Investigación- Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Lima, Peru,* [2]*Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA,* [3]*Universidad Nacional de Cajamarca, Facultad de Medicina, Cajamarca, Peru,* [4]*SYNAPSIS Mental Health and Neurology Non-Profit organization, Lima, Peru,* [5]*Universidad Peruana Cayetano Heredia, Facultad de Medicina. Lima, Peru, Lima, Peru.*

244. Facial Pain Caused by a Traumatic Inferior Alveolar Nerve Neuroma Detected after Exploratory Surgery Despite Normal Imaging Findings

***Mauricio X. Perez, MD**, Andrea Gil-Guevara, MD, Chilvana Patel, MD, Hisham Marwan, MD, Gerald Campbell, MD. UTMB, Galveston, TX, USA.*

245. Case Report: Stroke and Status Epilepticus as Complications of Lumbar Epidural Steroid Injection; a Cascade of Catastrophe

***Michael Beeler, DO**, Kevin Cannard, MD. Walter Reed National Military Medical Center, Bethesda, MD, USA.*

Traumatic Brain Injury

246. Diffusion Tensor Magnetic Resonance Imaging of Hypothalamus in Traumatic Brain Injury Warfighters with Sleep Dysfunction

J. Kent Werner, Jr., MD, PhD[1], *Brian Gerstenslager, MD, PhD*[1], *Ping-Hong Yeh, PhD*[2], *Rujirutana Srikanchana, PhD*[2], *Kimbra Kenney, MD*[1], *John Ollinger, PhD*[2]. [1]*Uniformed Services University, Bethesda, MD, USA,* [2]*Walter Reed National Military Medical Center, Bethesda, MD, USA.*

247. Age and Sex Moderate Effects of ABCC8 and TRPM4 Genetic Variability on Traumatic Intracerebral Hemorrhage Progression

*Benjamin Zusman, BSc, Patrick Kochanek, MD, Ava Puccio, PhD, David Okonkwo, MD PhD, Yvette Conley, PhD, Shashvat Desai, MBBS, Matthew Leach, MD, **Ruchira M. Jha, MD MSc**. University of Pittsburgh, Pittsburgh, PA, USA.*

248. Low-Field, Point-of-Care Magnetic Resonance Imaging of Subdural Hematoma

Mercy H. Mazurek, BS[1], *Matthew M. Yuen, BA*[1], *Bradley A. Cahn, BS*[1], *Jill T. Shah, BS*[1], *Samantha By, PhD*[2], *Houchun Harry Hu, PhD*[2], *E. Brian Welch, PhD, MBA*[2], *Carole Lazarus, PhD*[2], *Hadrien Dyvorne, PhD*[2], *Adrienne Ward, RN*[3], *Nona Timario, MSN*[3], *Guido J. Falcone, MD, ScD, MPH*[1], *Barbara Gordon-Kundu, MD, BSN*[1], *Emily J. Gilmore, MD*[1], *David Y. Hwang, MD*[1], *Jennifer A. Kim, MD, PhD*[1], *Firas Kaddouh, MD*[1], *Kevin Gobeske, MD, PhD, MPH*[1], *Richa Sharma, MD, MPH*[1], *Joseph Schindler, MD*[1], *Charles Matouk, MD*[1], *Ryan Hebert, MD*[1], *Charles Wira, MD*[1], *Gordon Sze, MD*[1], *Matthew S. Rosen, PhD*[4], *W. Taylor Kimberly, MD, PhD*[4], *Kevin N. Sheth, MD*[1]. [1]*Yale School of Medicine, New Haven, CT, USA,* [2]*Hyperfine Research, Inc, Guilford, CT, USA,* [3]*Yale New Haven Hospital, New Haven, CT, USA,* [4]*Harvard Medical School, Boston, MA, USA.*

249. Investigating the Role of the Claustrum in Consciousness Recovery Following Severe Brain Injury

Adeeb Narangoli, Medical Student[1], *Esteban A. Fridman, MD, PhD*[2], *Nicholas Schiff, BA, MD*[2]. [1]*Weill Cornell Medicine - Qatar, Doha, Qatar,* [2]*Weill Cornell Medicine, New York, NY, USA.*

250. Lack of Efficacy of Stem Cells in the Treatment of Chemosensory Dysfunction

Ibrahim Farah, MD[1], *Matheus Otero, MD*[2], *Domenico Schirripa, MD*[3], *Tabinda Qamar, MD*[4], *Alan R. Hirsch, MD*[5]. [1]*WIndsor University School of Medicine, St.Kitts, Saint Kitts and Nevis,* [2]*Universidade Salvador (UNIFACS), Salvador, Brazil,* [3]*Xavier University School of Medicine, Oranjestad, Aruba,* [4]*Aureus University School of Medicine, Oranjestad, Aruba,* [5]*Smell & Taste Treatment and Research Foundation, Chicago, IL, USA.*

251. Poor Sleep after Mild Traumatic Brain Injury is Associated with Increased Inflammation in Warfighters

Josephine U. Pucci, BA[1], *Sara M. Mithani, PhD*[2], *Jackie Leete, BA*[2], *Risa Nakase-Richardson, PhD*[3,4], *Chen Yai, PhD*[2], *Kimbra Kenney, MD*[1], *Jessica Gill, PhD*[2], *John Kent Werner, MD PhD*[1,5]. [1]*Uniformed Services University, Bethesda, MD,*

USA, [2]National Institute of Health, Bethesda, MD, USA, [3]University of South Florida, Tampa, FL, USA, [4]Defense and Veterans Brain Injury Center, Tampa, FL, USA, [5]Center for Neuroscience and Regenerative Medicine, Bethesda, MD, USA.

252. Longitudinal Changes in Cerebral Blood Flow after Traumatic Brain Injury

***Linda Xu, BA**[1], Jeffrey B. Ware, MD[1], Junghoon J. Kim, PhD[2], Erika Silverman, BS[1], Brigid Magdamo, BA[1], Cian Dabrowski, MS[1], Leroy Wesley, BS[1], My Duyen Le, BS[1], Justin Morrison, BA[1], Hannah Zamore, AB[1], Ramon Diaz-Arrastia, MD, PhD[1], Danielle K. Sandsmark, MD, PhD[1]. [1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA, [2]The City College of New York, New York City, NY, USA.*

253. Post-Traumatic Exercise-Induced Pseudo-Cerebrospinal Fluid Rhinorrhea

***Matheus Otero, BS**[1], Domenico Schirripa, BS[2], Tabinda Qamar, BS[3], Ibrahim Farah, BS[4], Alan R. Hirsch, MD[5]. [1]Universidade Salvador (UNIFACS), Salvador, Brazil, [2]Xavier University School of Medicine, Oranjestad, Aruba, [3]Aureus University School of Medicine, Oranjestad, Aruba, [4]Windsor University School of Medicine, Saint Kitts, Saint Kitts and Nevis, [5]Smell and Taste Treatment and Research Foundation, Chicago, IL, USA.*

254. Paroxysmal Sympathetic Hyperactivity Syndrome in Severe Traumatic Brain Injury: Patient Characteristics, Utilization of Sedation, Analgesia and Anesthetic Intravenous Infusion Medications and Patient Outcome

*Rebekah Proctor, Medical Student, Sherry Stephens-Gibson, DrPH, MPH, MCHES, Lucy Paticia McEuen, PharmD, Kyla Leon, PharmD, **Christa Nobleza, MD**. University of Mississippi Medical Center, Jackson, MS, USA.*

255. Diffusion Tensor Imaging Correlates of Concussion Related Cognitive Impairment

*Angelica C. Cornejo, MD[1], **Minseon Kim, MD**[1], Zafer Keser, MD[1], Lamya Ibrahim, MD[1], Sonia K. Singh, MD[1], Mohammad J. Ahmad, MD[1], Omar Hasan, MS[1], Khader M. Hasan, PhD[2], Paul E. Schulz, MD[1]. [1]University of Texas McGovern Medical School, Departments of Neurology, Houston, TX, USA, [2]University of Texas McGovern Medical School, Department of Diagnostic and Interventional Radiology, Houston, TX, USA.*

K-588. ABCC8 and TRPM4 Genetic Variability is Associated with Intracerebral Hemorrhage Progression after Severe Traumatic Brain Injury

*Benjamin E. Zusman, BS, Patrick M. Kochanek, MD, Ava M. Puccio, PhD, David O. Okonkwo, MD PhD, Matthew Leach, MD, Shashvat M. Desai, MBBS, Yvette P. Conley, PhD, **Ruchira M. Jha, MD MSc**. University of Pittsburgh, PITTSBURGH, PA, USA.*

K-592. Selective Inhibitory Circuit Dysfunction in the Orbitofrontal Cortex is Associated with Cognitive Inflexibility after Traumatic Brain Injury

***Amber Nolan**[1], Vikaas Sohal, MD PhD[2], Susanna Rosi, PhD[2], Susanna Rosi, PhD[2]. [1]University of California San Francisco, [2]University of California San Francisco, San Francisco, CA, USA.*

Tuesday Poster Presentations

Cerebrovascular Disease

256. Is Motor Recovery after Ischemic Stroke Proportional? Consideration on Ceiling Effect of Fugl-Meyer Assessment Scale

***Hyun Haeng Lee, M.D., M.S.**[1], Jongmin Lee, M.D., Ph.D.[1], Yun-Hee Kim, M.D., Ph.D.[2]. [1]Konkuk University Medical Center, Seoul, Korea, Republic of, [2]Samsung Medical Center, Seoul, Korea, Republic of.*

257. Decline in Stroke Alerts and Hospitalizations During the COVID-19 Pandemic

***Malveeka Sharma, MD, MPH**[1], Vasileios Lioutas, MD[2], Tracy Madsen, MD, ScM[3], Judith Clark, RN[4], Jillian O'Sulluvan, RN[2], Tina M. Burton, MD[3], Amelia Boehme, PhD[5], Hugo J. Aparicio, MD, MPH[4]. [1]University of Washington, Seattle, WA, USA, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA, [3]Brown University, Providence, RI, USA, [4]Boston University Medical Center, Boston, MA, USA, [5]Vagelos College of Physicians and Surgeons, Columbia University, New York City, NY, USA.*

258. Polypill Trials for Stroke Prevention — Main Results, Critical Appraisal, and Implications for US Population

***Mam Ibraheem, MD, MPH**, Larry B. Goldstein, MD, FAAN, FANA, FAHA. University of Kentucky, Lexington, KY, USA.*

259. Retrospect Diagnosis of Hypoxic-Ischemic Cortical Blindness in a Patient Manifesting with Presumed Nonorganic Vision Loss — Case Presentation and Lessons Learned

*Chintan Rupareliya, MD, Tarek Ali, MD, **Mam Ibraheem, MD, MPH**. University of Kentucky-Department of Neurology, Lexington, KY, USA.*

260. Adapting a Stroke Preparedness Music Video for a High Stroke Risk Population

***Mellanie V. Springer, MD MS**, Nishat Islam, MPH, Lesli E. Skolarus, MD MS. University of Michigan, Ann Arbor, MI, USA.*

261. FLAIR Hyperintense Vessel Rating to Predict Penumbra in Acute Stroke

***Alexandra Walker, BA**, Lisa Bunker, PhD, CCC-SLP, Richard Leigh, MD, Erin Meier, PhD, CCC-SLP, Emily Goldberg, MS, CCC-SLP, Argye Hillis, MD, MA. Johns Hopkins University School of Medicine, Baltimore, MD, USA.*

262. Appearance of Intracerebral Hemorrhage on Low-Field, Point-of-Care Magnetic Resonance Imaging

***Mercy H. Mazurek, BS**[1], Bradley A. Cahn, BS[1], Matthew M. Yuen, BA[1], Jill T. Shah, BS[1], Samantha By, PhD[2], Houchun Harry Hu, PhD[2], E. Brian Welch, PhD, MBA[2], Rafael O'Halloran, PhD[2], Adrienne Ward, RN[3], Nona Timario, MSN[3], Guido J. Falcone, MD, ScD, MPH[1], Emily J. Gilmore, MD[1], David Y. Hwang, MD[1], Barbara Gordon-Kundu, MD, BSN[1], Jennifer A. Kim, MD, PhD[1], Firas Kaddouh, MD[1], Kevin Gobeske, MD, PhD, MPH[1], Richa Sharma, MD, MPH[1], Joseph Schindler, MD[1], Charles Matouk, MD[1], Ryan M. Hebert, MD[1], Charles Wira, MD[1], Gordon Sze, MD[1], Matthew S. Rosen, PhD[4], W. Taylor Kimberly, MD, PhD[4], Kevin N. Sheth, MD[1]. [1]Yale School of Medicine, New Haven, CT, USA, [2]Hyperfine Research, Inc, Guilford, CT, USA, [3]Yale New Haven Hospital, New Haven, CT, USA, [4]Harvard Medical School, Boston, MA, USA.*

263. Mortality Risk Stratification in Pediatric Ischemic Stroke: Analysis of 4,036 Inpatients in The United States

***Nitya Beriwal, MBBS**[1], Rikinkumar S. Patel, MD, MPH[2]. [1]Lady Hardinge Medical College, New Delhi, India, [2]Griffin Memorial Hospital, Norman, OK, USA.*

264. Burden and Outcomes of Acute Ischemic Stroke among End Stage Renal Disease Patients: A National Perspective

***Urvish Patel, MBBS, MPH**[1], Achint Patel, MD, MPH[2], Reshmi Adupa, MBBS[3], Khin Tun, MBBS[4], Sukrut Pagad, MD[5], Prerna Agrawal, MBBS[6], Gurjot Grewal, MBBS[7], Abhishek Lunagariya, MD, MHA[1]. [1]Creighton University School of Medicine, Omaha, NE, USA, [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Garden City Hospital, Garden City, MI, USA, [4]University of Medicine 2, Yangon, Myanmar, [5]Larkin Community Hospital, Hialeah, FL, USA, [6]DY Patil University School Of Medicine, Mumbai, India, [7]Christian Medical College, Ludhiana, India.*

265. Corneal Confocal Microscopy: Corneal Nerve Loss in Acute Stroke Patients with Poor Pial Collaterals

***Ajay Menon, MD Candidate**[1], Adnan Khan, PhD[1], Saadat Kamran, MD[2], Naveed Akhtar, FCPS[2], Georgios Ponirakis, MPhil[1], Ioannis N. Petropoulos, PhD[1], Hoda Gad, MSc[1], Ahmad Muhammad, MD[2], Maher Saqqur, MD[2,3], Pablo G. Bermejo, MD[1], Paula Bourke, MSc[2], Deborah Morgan, MSc[2], Mark Santos, PhD[2], Ashfaq Shuaib, MD[2,3], Rayaz A. Malik, MB ChB, PhD[1]. [1]Weill Cornell Medicine - Qatar, Doha, Qatar, [2]Institute of Neuroscience, Hamad General Hospital, Doha, Qatar, [3]Department of Medicine, University of Alberta, Edmonton, AB, Canada.*

266. Optimizing the Evaluation and Treatment of In-Hospital Stroke

***Christopher Parrino, BA**[1], Aaron Noles, MD[2], Rakhee Lalla, DO[2], Prachi Mehndiratta, MBBS[2], Michael Phipps, MD[2], Carolyn Cronin, MD, PhD[2], John Cole, MD[2], Marcella Wozniak, MD, PhD[2], Karen Yarbrough, DNP[2], Seemant Chaturvedi, MD[2]. [1]University of Maryland School of Medicine, Baltimore, MD, USA, [2]University of Maryland Medical Center, Baltimore, MD, USA.*

267. Horizontal Titibations with Alternating Movements

***Domenico Schirripa, Medical Doctorate**[1,2]. [1]Xavier University School of Medicine, Oranjestad, IL, USA, [2]Xavier University School of Medicine, Oranjestad, Aruba.*

268. The Influence of Metabolic Syndrome on Gray Matter Volume in Early, Young, and Middle-Aged Mexican-American Adults

***Eithan Kotkowski, PhD**[1], Larry Price, PhD[2], Ralph DeFronzo, MD[1], Franklin Crystal, MS[1], Franklin Crystal, MS[1], Maximino Salazar, BS[1], Amy Garrett, PhD[1], Mary Woolsey, MS[1], John Blangero, PhD[3], David Glahn, PhD[4], Peter Fox, MD[1]. [1]UT Health Science Center at San Antonio, San Antonio, TX, USA, [2]Texas State University, San Marcos, TX, USA, [3]UT Rio Grande Valley, Brownsville, TX, USA, [4]Yale School of Medicine, New Haven, CT, USA.*

269. Domain-Specific Cognitive Performance after Incident Stroke: The Northern Manhattan Study

***Michelle R. Caunca, PhD**[1], Clinton B. Wright, MD, MS[2], Marialaura Simonetto, MD, MS[3], Ying Kuen Cheung, PhD[4], Mitchell S.V. Elkind, MD, MS[4], Tatjana Rundek, MD, PhD[1], Ralph L. Sacco, MD, MS[1]. [1]University of Miami Miller School of Medicine, Miami, FL, USA, [2]National Institute of Neurological Disease and Stroke, Bethesda, MD, USA, [3]Cornell University, New York, NY, USA, [4]Columbia University, New York, NY, USA.*

270. Could Ischemic Stroke Infarct Volume Aid in Determining Stroke Subtype?

***Nicholas O. Daneshvari, B.A.**, Michelle C. Johansen, M.D., Ph.D. Johns Hopkins School of Medicine, Baltimore, MD, USA.*

271. Stumped by Recurrent Strokes? Think of "Stump" Syndrome!

***Walter S. Rose, BS**, Prashant A. Natteru, MD, Alexander P. Auchus, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

272. Adapting Reach Out: A Mobile Health Intervention Trial, in Response to the Coronavirus Pandemic

Candace O. Whitfield, Bachelors of Science, *Mackenzie Dinh, Master of Public Health, William Meurer, Doctor of Medicine, Zahera Farhan, Masters of Public Health, Lesli Skolarus, Doctor of Medicine. University of Michigan, Ann Arbor, MI, USA.*

273. Cardiac Structure and Function is Associated with Hemispatial Neglect Severity

Nicole L. Williams, MS, *Adrian Suarez, BS, Serban Negoita, BS, Argye Hillis, MD, MA, Rebecca F. Gottesman, MD, PhD, Michelle C. Johansen, MD, PhD. The Johns Hopkins University School of Medicine, Baltimore, MD, USA.*

274. Asymptomatic Giant Tumefactive Perivascular Spaces- An Incidental Finding

Pretty Sara Idiculla, MBBS[1], *Dhineshreddy Gurala, MBBS*[2], *Junaid Habib Siddiqui, MD*[1]. [1]*University of Missouri, Columbia, MO, USA,* [2]*Staten Island University Hospital, Northwell Health, Staten Island, NY, USA.*

275. Regional Assessment of Cerebral Microvascular Disease (RACMD) Score: A Clinical MRI Grading System

Saman Hazany, MD[1], *Kim L. Nguyen, MD*[1], *Benjamin Ellingson, PhD*[2], *Martin Lee, PhD, CStat, CSci, FIBMS*[1], *Jason D. Hinman, MD, PhD*[1]. [1]*Greater Los Angeles VA Healthcare System and David Geffen School of Medicine at UCLA, Los Angeles, CA, USA,* [2]*David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.*

276. Altered Brain Network Dynamics in Stroke Predict Behavior

Chiara Favaretto, PhD[1], *Michele Allegra, PhD*[2], *Andrea Brovelli, PhD*[2], *Gustavo Deco, PhD*[3], *Maurizio Corbetta, MD*[1]. [1]*Dept.Neuroscience, Padova Neuroscience Ctr. University of Padova, Padova, Italy,* [2]*Institut de Neurosciences de la Timone, Marseille, France,* [3]*Universitat Pompeu Fabra; Institució Catalana de la Recerca i Estudis Avançats, Barcelona, Spain.*

277. Association between Hematoma Characteristics and Risk of Uncontrolled Blood Pressure in Intracerebral Hemorrhage Survivors

Evangelos Pavlos Myserlis, MD[1,2], *Kay-Cheong Teo, MBBS, FHKAM5*[3], *Bailey E. Montgomery, BS*[1,2], *Jessica Abramson, BA*[1,2], *Lansing Sugita, BS*[2,4], *Andrew D. Warren, BS*[4], *Joshua N. Goldstein, MD, PhD*[5], *M. Edip Gurol, MD, MSc*[4], *Anand Viswanathan, MD, PhD*[4], *Steven Greenberg, MD, PhD*[4], *Alessandro Biffi, MD*[2,4], *Christopher D. Anderson, MD, MMSc*[1,2], *Jonathan Rosand, MD, MSc*[1,2]. [1]*Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA,* [2]*Henry and Allison McCance Center for Brain Health, Massachusetts General Hospital, Boston, MA, USA,* [3]*Department of Medicine, Queen Mary Hospital, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong,* [4]*Department of Neurology, Massachusetts General Hospital, Boston, MA, USA,* [5]*Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA.*

278. Hippocampal Cellular Changes in the Three-Vessel Model of Global Ischemia in Rat

Tatyana Anan'ina, PhD[1], *Alena Kisel, PhD*[1], *Marina Kudabaeva, M.S.*[1], *Galina Chernysheva, PhD*[2], *Vera Smolyakova, PhD*[2], *Elena Krutenkova, PhD*[1], *Konstantin Usov, PhD*[1], *Mark Plotnikov, PhD*[2], *Marina Khodanovich, PhD*[1]. [1]*Tomsk State University, Tomsk, Russian Federation,* [2]*Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk, Russian Federation.*

279. The Need for Advanced Neuroimaging in Acute Ischemic Stroke: Lessons from a Multi-Year Retrospective Analysis at a Comprehensive Stroke Center

Joseph Conovaloff, MS3[1], ***Amit Chaudhari, MD PhD***[2], *Mohammed Shafie, MD PhD*[1]. [1]*University of California Irvine, Anaheim, CA, USA,* [2]*University of California Irvine, Orange, CA, USA.*

280. A Case of Transient Cerebral Edema Following Endovascular Repair of Basilar-Tip Aneurysm Using Double-Catheter Technique

Andrea Gil-Guevara, MD, *Mauricio Perez-Davila, MD, Neeharika Thottempudi, MD, Hashem Shaltoni, MD, Anand Patel, MD, Karthikram Raghuram, MD. UTMB, Galveston, TX, USA.*

281. The Low Dimensional Structure of Neurological Impairment in Stroke

Antonio Luigi Bisogno, MD[1,2], *Elena Monai, MD*[1,2], *Chiara Favaretto, PhD*[1,2], *Andrea Zangrossi, PhD*[1,2], *Silvia Facchini, PhD*[1], *Serena De Pellegrin, Speech Therapist*[1], *Marco Castellaro, PhD*[3], *Annamaria Basile, MD*[4], *Claudio Baracchini, MD*[5], *Maurizio Corbetta, MD,PhD*[1,2]. [1]*University of Padova, Padova, Italy,* [2]*Padova Neuroscience Center, Padova, Italy,* [3]*University of Verona, Verona, Italy,* [4]*S.Antonio Hospital of Padova, Padova, Italy,* [5]*Azienda Ospedaliera di Padova, Padova, Italy.*

282. Diffusion: Not All Diffusion Restrictive Lesions on MRI Suggest an Acute Infarct

Ayush Singh, MD, *Neeharika Thottempudi, MD, Chilvana Patel, MD, Hashem Shaltoni, MD, Anand Patel, MD. UTMB, Galveston, TX, USA.*

283. Challenges and Approach to the Diagnosis of Spinal Cord Infarction

Ayush Singh, MD, *Varun Shah, MD, Chilvana Patel, MD. UTMB, Galveston, TX, USA.*

284. Dietary Supplements in Stroke Prevention: A Review of Recent Literature

***Christopher Smith, MD**, Alan Velander, MD. LSU HSC, New Orleans, LA, USA.*

285. Cerebral Air Embolism Complicating Atrio-Esophageal Fistula in Williams Syndrome

***Dana Ionel, DO**[1], Fred Odago, MD[1], A E. Ene, MD[2], William N. O'Connor, MD[2], Jessica D. Lee, MD[1], Luther C. Pettigrew, MD, MPH[1]. [1]Department of Neurology, University of Kentucky Chandler Medical Center, Lexington, KY, USA, [2]Department of Pathology & Laboratory Medicine, University of Kentucky Chandler Medical Center, Lexington, KY, USA.*

286. Lateral Lesion: A Case of Wallenberg Syndrome

***Dhivya Pahwa, MD**[1], Ernai Hernandez-Sanchez, MD[1], Wazhma Hossaini, MD[1], Hos Loftus, MD[2]. [1]Long Island Community Hospital, Patchogue, NY, USA, [2]South Shore Neurology Associates, P.C., Patchogue, NY, USA.*

287. Reversible Cerebral Vasoconstriction Syndrome in a Patient Sprayed by Oleoresin Capsicum "Pepper Spray"

***Dmitri Kovalev, MD**, Neeharika Thottempudi, MD, Chilvana Patel, MD, Hashem Shaltoni, MD, Karthikram Raghuram, MD, Anand V. Patel, MD. University of Texas Medical Branch, Galveston, TX, USA.*

288. New Onset Cervical Dystonia after Resolving Posterior Reversible Encephalopathy Syndrome (PRES): A Case Report and Literature Review

***Elham Azizi, MD**, Julia Staisch, MD, Osvaldo Camilo, MD. Ochsner Medical Center, New Orleans, LA, USA.*

289. A Case of Charles Bonnet Syndrome Following Anoxic Brain Injury

***Gaurav Kathuria, MD**, Christian Bachelor, MD. Memorial Healthcare System, Pembroke Pines, FL, USA.*

290. Anatomical Substrate of QTc Prolongation in Acute Medullary Infarction

***Goun Je, MD-PhD**[1], Yuyao Sun, MD[1], Kiandokht Keyhanian, MD[1], Nils Henninger, MD, PhD, Dr med[1,2]. [1]Department of Neurology, University of Massachusetts Medical School, Worcester, MA, USA, [2]Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA.*

291. Small Fiber Neuropathy Mimicking Stroke, a Case of Adie Tonic Pupil of as a Consequence of Long Standing Small Fiber Neuropathy

***Hibatullah Abu El-Haija, MD**, Ayush Singh, MD, Chilvana Patel, MD. UTMB, Galveston, TX, USA.*

292. A Case of Venous Loop Causing Glossopharyngeal Neuralgia

***Hibatullah Abu El-Haija, MD**, Chilvana Patel, MD. UTMB, Galveston, TX, USA.*

293. Difference in Inpatient Clinical Outcomes of Acute Ischemic Stroke Patients Based on Brain MRI Utilization

***Hwan Lee, MD**[1,2], Yifeng Yang, MD[2], Baoqiong Liu, MD PhD[3], Simon Castro, MD[2], Tiantian Shi, MD[4]. [1]Hospital of the University of Pennsylvania, Philadelphia, PA, USA, [2]St. Vincent's Medical Center, Bridgeport, CT, USA, [3]Florida Hospital Medical Group, Orlando, FL, USA, [4]Bridgeport Hospital, Bridgeport, CT, USA.*

294. Association between Baseline Cognitive Function and Functional Outcome Change after Ischemic Stroke

***Jae Kyung Chung, Medical Master**, Sunghun Kim, Master, Yeshin Kim, Master. Kangwon National University Hospital, Chuncheon, Korea, Republic of.*

295. Limb Shaking Ischemia and Vertebral Artery Stenosis

***Kristina Maselli, MD**, Sydney Moseley, MD, Ramandeep Sahni, MD. Westchester Medical Center, Valhalla, NY, USA.*

296. A Case of an Embolic Stroke Following Mesenteric Arteriogram

***Lalitha Battineni, MD**, Ruiqing L Sun, MD,PHD, Anand Patel, MD, Hashem Shaltoni, MD. UTMB, Galveston, TX, USA.*

297. Atypical Leukoencephalopathic Changes with Chronic Methamphetamine Abuse

***Madiha Tariq, MD**, Bhanu Gogia, MD, Arun Chhabra, MD. UTMB, Galveston, TX, USA.*

298. Excessive Caffeine Intake from Energy Supplements as a Cause of Ischemic Stroke in Young Patients

***Madiha Tariq, MD**, Gogia Bhanu, MD, Arun Chhabra, MD. UTMB, Galveston, TX, USA.*

299. Cerebral Venous Sinus Thromboses (CVST) with Stroke Symptoms in a Patient with Controlled Ulcerative Colitis

***Madiha J. Tariq, MD**, Yanis R. Amrani, MD, Anand Patel, MD, Hashem Shaltoni, MD. UTMB, Galveston, TX, USA.*

300. Bilateral Acute Ischemic Stroke: Rare Case of Bilateral Internal Carotid Artery Hypoplasia

***Maria Shoaib, MD**, Sara Habib, MD, Ahmer Asif, MD, Ahmed Eid Abdelkader, MD, Ahmad A. Al Awwad,*

MD. Department of Neurology, University of Oklahome Health Sciences Center, Oklahoma City, OK, USA.

301. Impact of COVID-19-Related Physical Distancing on Mental and Physical Health of People with Recent Stroke

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302. Spontaneous Vertebrobasilar Artery Dissection in a Patient with Ankylosing Spondylitis: An Association or a Co-Incidence?

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303. Munchausen Syndrome by Tissue Plasminogen Activator (tPA): Patients Seeking Thrombolytic Administration

Rafer Willenberg, MD, PhD*, Bo Leung, MD, Shlee Song, MD, Oana M. Dumitrascu, MD, MSc, Konrad Schlick, MD, Patrick Lyden, MD. Cedars-Sinai Medical Center, Los Angeles, CA, USA.*

304. Comparison of Functional Outcome after Mechanical Thrombectomy between Diabetic and Non-Diabetic Patients

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305. Stroke Epidemiology in Adults with HIV Infection in Zambia

Stanley Zimba, MBChB, MMed*. University Teaching Hospital, Lusaka, Zambia.*

306. Human Plasma Proteomics for Biomarker Discovery for Ischemic Stroke and Transient Ischemic Attack

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307. Diffusion Tensor Imaging Profiles of Thalamic Nuclei and Thalamocortical Pathways and Their Role in Naming after Stroke

Zafer Keser, MD[1,2], *Erin L. Meier, PhD, CCC-SLP*[2], *Melissa D. Stockbridge, PhD, MSc*[2], *Rajani Sebastian, PhD*[2], *Argye E. Hillis, MD, MA*[2]. [1]*University of Texas Health Science Center at Houston, Department of Neurology, Houston, TX, USA,* [2]*Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA.*

308. Correction of the Edema Effect on the Myelin Content Estimation Using Macromolecular Proton Fraction (MPF) Mapping in a Rat Ischemic Stroke Model

Marina Kudabaeva, M.S.[1], *Marina Khodanovich, PhD*[1], *Vlad Schwartz, B.S.*[1], *Alena Kisel, PhD*[1], *Ilya Gubskiy, M.D.*[2], *Darya Namestnikova, M.D.*[2], *Vasily Yarnykh, PhD*[3]. [1]*Tomsk State University, Tomsk, Russian Federation,* [2]*Pirogov Russian National Research Medical University, Moscow, Russian Federation,* [3]*University of Washington, Seattle, WA, USA.*

K-582. Identifying Patients with Intracerebral Hemorrhage Who May Forego Intensive Care Unit Admission: A Novel Risk Score in the COVID-19 Era

Romanus Faigle, MD, PhD[1], *Bridget Chen, BS*[1], *Rachel Kreiger, BS*[1], *Elisabeth B. Marsh, MD*[1], *Ayham M. Alkhachroum, MD*[2], *Wei Xiong, MD*[3], *Victor C. Urrutia, MD*[1], *Rebecca F. Gottesman, MD, PhD*[1]. [1]*Johns Hopkins University, Baltimore, MD, USA,* [2]*University of Miami, Miller School of Medicine, Jackson Memorial Health System, Miami, FL, USA,* [3]*Case Western Reserve University School of Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH, USA.*

K-583. Bedside Optical Monitoring of Microvascular Reperfusion during Endovascular Thrombectomy

Christopher G. Favilla, MD[1], *Rodrigo M. Forti, PhD*[2], *Wesley B. Baker, PhD*[3], *John A. Detre, MD*[1], *Scott E. Kasner, MD*[1], *David Kung, MD*[1], *Arjun G. Yodh, PhD*[1]. [1]*University of Pennsylvania, Philadelphia, PA, USA,* [2]*Institute of Physics, University of Campinas, Sao Paulo, Brazil,* [3]*Childrens Hospital of Philadelphia, Philadelphia, PA, USA.*

K-586. Infarcts are Associated with Globally Decreased Cortical Thickness in Children with Sickle Cell Disease

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Interventional Neurology

309. Hypesthetic Ataxic Hemiparesis: Thinking Beyond the Conventional Paradigm

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310. Post-Lumbar Puncture Retroperitoneal Hematoma

Maria J. Abraham, B.S.*, Yousaf Ajam, MD, Xiang Fang, MD, PhD, FAAN, FANA. University of Texas Medical Branch at Galveston, Galveston, TX, USA.*

311. Safety of Cerebral Angiography in Private Outpatient Clinical Setting

***Seyed Mostafa Razavi, MD**, Edrick Masangkay, MD, Nikhila Chelikam, MD, Ursula Kelly-Tolley, RN, Lindsey Pierce, MD, Reza Malek, MD, Arash Padidar, MD. Minimally Invasive Surgical Solutions, San Jose, CA, USA.*

312. Outcomes for Inter-Hospital Transfer versus Direct Admit Patients Undergoing Stroke Thrombectomy

***Cassie Nankee, M.D.**, Colin Smith, BS, Eyad Almallouhi, M.D., Sami Al Kasab, MD, Christine A. Holmstedt, D.O. Medical University of South Carolina, Charleston, SC, USA.*

313. Process Improvement: Streamlining Cognitive Evaluation of Stroke Patients Treated with Mechanical Thrombectomy

***Muhammad-Atif Zubairi, MD**, Jessica D. Lee, MD, Justin F. Fraser, MD. University of Kentucky, Lexington, KY, USA.*

314. Acute Interventions for In-Hospital Stroke Patients

***Rakhee Lalla, DO**, Christopher Parrino, BA, Karen Yarbrough, CRNP, Prachi Mehndiratta, MD, Michael Phipps, MD, Carolyn Cronin, MD, PhD, Marcella Wozniak, MD, PhD, John Cole, MD, MS, Seemant Chaturvedi, MD. University of Maryland Medical Center, Baltimore, MD, USA.*

315. Bilateral Thalamic Venous Edema Associated with Unruptured Arteriovenous Malformation Corrected with Endovascular Therapy: A Case Report and Literature Review

***Sergio Taborda, Neurology**[1], Julián Cuartas, Neurology[1], Jorge Pulgarin, Neurointerventional Surgeon[2], Catalina Trujillo, Medical Doctor[3]. [1]Neurological Institute of Colombia and CES University, Medellín, Colombia, [2]Neurological Institute of Colombia, Medellín, Colombia, [3]Autonomous University Foundation of the Americas, Pereira, Colombia.*

Neurocritical Care

316. Dynamic Changes in Brain and Body Variables Predict Recovery in Acute Traumatic Brain Injury Coma

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317. MRI Findings in Acute Hyperammonemic Encephalopathy Secondary to Acetaminophen Toxicity

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318. A New Normal after Severe Acute Brain Injury: An Observational Cohort Using a Sequential Explanatory Design

*Rachel Rutz Voumard, MD[1,2], Whitney Kiker, MD[1], Kaley Dugger, BS[1], Ruth Engelberg, PhD[1], Giandomenico Borasio, MD[2], J Randall Curtis, MD[1], Ralf Jox, MD[2], **Claire Creutzfeldt, MD**[1]. [1]University of Washington, Seattle, WA, USA, [2]CHUV, Lausanne, Switzerland.*

319. Models Integrating Epileptiform Abnormalities, TCD, and Clinical Variables Improve DCI Prediction after SAH

***Hsin Yi Chen, BS**[1], Jonathan Elmer, MD[2], Manohar Ghanta, MS[3], Junior Valdery-Moura, MS[3], Eric S. Rosenthal, MD[3], Sahar F. Zafar, MD[3], Emily J. Gilmore, MD[4], Lawrence J. Hirsch, MD[4], Kevin N. Sheth, MD[4], Nils H. Petersen, MD/PhD[4], M. Brandon Westover, MD/PhD[3], Jennifer A. Kim, MD/PhD[4]. [1]Yale School of Medicine, New Haven, CT, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Yale New Haven Hospital, New Haven, CT, USA.*

320. Characterizing Blunt Cerebrovascular Injuries and Stroke: A Single Center Retrospective Study

***Lillie Tien, B.S.**, Dan-Victor Giurgiutiu, M.D., Erin Switzer, D.O., Jeffrey Switzer, D.O. Medical College of Georgia, Augusta, GA, USA.*

321. Effects of HIV on T1w/T2w Cortical Myelin

***Beau M. Ances, MD, Ph.D**, Dimitre N. Tomov, MS, Jeremy F. Strain, Ph.D, Sarah M. Cooley, Ph.D., Anna A. Boerwinkle, BS. Washington University in Saint Louis, Saint Louis, MO, USA.*

322. Comparison of Optic Nerve Sheath Diameter as a Non Invasive Measurement of Raised Intracranial Pressure with Ventricular Catheter in 51 Patients - An Exclusive Neurocritical Care Institutional Experience

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323. Neurologic Consequences of Covid-19 Coronavirus Infection Correspond to ACE2 Receptor At1 Proinflammatory and Procoagulant Responses

***Robert L. Knobler, MD, PhD**. Knobler Institute of Neurologic Disease, Fort Washington, PA, USA.*

324. Intracerebral Hemorrhage and Clinical Outcome on Low Field, Portable, Point-of-Care Magnetic Resonance Imaging

***Matthew M. Yuen, BA**[1], Bradley A. Cahn, BS[1], Mercy H. Mazurek, BS[1], Jill T. Shah, BS[1], E. Brian Welch, PhD, MBA[2], Samantha By, PhD[2], Houchun Harry Hu, PhD[2],*

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325. Quetiapine Use in the Neurocritical Care Setting

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326. Peri-Arrest Characteristics and Outcomes in Overdose-Related Cardiac Arrest

***Stephanie Liang, M.D.**[1], Jonathan A. Duskin, M.D.[2], Katie K. Dam, B.A.[3], Kushak Suchdev, M.D.[3], William Spears, M.D.[3], David M. Greer, M.D.[3,1]. [1]Boston University School of Medicine, Boston, MA, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]Boston Medical Center, Boston, MA, USA.*

327. Can Lateralized Periodic Discharges Serve as a Prognostic Tool in Soporific Acute Hyperammonemic Encephalopathy (AHE)?

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328. Percutaneous Coronary Intervention Complicated by Anterior Spinal Cord Infarction

***Sushant Puri, MBBS**[1], Eric Zhang, BS[2]. [1]University of Illinois at Chicago, Chicago, IL, USA, [2]Chicago Medical School, Rosalind Franklin University of Medicine and Science, Chicago, IL, USA.*

K-577. Determinants of Functional Brain Connectivity after Subarachnoid Hemorrhage

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K-581. Early Prediction of Time-to-Awakening after Cardiac Arrest

***Jonathan Elmer, MD, MS**, Kate Flickinger, MS, Clifton W. Callaway, MD, PhD, Patrick J. Coppler, PA-C. University of Pittsburgh, Pittsburgh, PA, USA.*

K-600. Anti-Seizure Drug Safety and Effectiveness in Aneurysmal Subarachnoid Hemorrhage

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Epilepsy

329. Automated EEG Self-Indexing Research Repository and Data Core

***Andres A. Rodriguez Ruiz, MD**, Nigel Pedersen, MD. Emory University, Atlanta, GA, USA.*

330. Patient Preferences for Treatment of Anxiety and Depression in an Adult Epilepsy Clinic

***Heidi Munger Clary, MD, MPH**, Rachel Croxton, MA, Beverly Snively, PhD, Gretchen Brenes, PhD, James Lovato, MS, Fatemeh Sadeghifar, BS, James Kimball, MD, Cormac O'Donovan, MD, Kelly Conner, PhD, PA-C, Esther Kim, BA, Jonathan Allan, MD, Pamela Duncan, PhD. Wake Forest School of Medicine, Winston-Salem, NC, USA.*

331. Marked Sleep Disruption in a Mouse Model of Medial Temporal Lobe Epilepsy

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332. Effects of Perampanel on Cognition & Quantitative Electroencephalography in Patients with Epilepsy

***Seon-Jae Ahn, M.D.**, Yong-Won Shin, M.D., Junsang Sunwoo, M.D., Ki-Young Jung, M.D., Sang Kun Lee, M.D., Kon Chu, M.D. Seoul National University Hospital, Seoul, Korea, Republic of.*

333. Rolandic Epilepsy is a Risk for Delay in Development of Visuospatial Functions and Kinesthetic Praxis in Children

***Sergey Kiselev, Ph.D.** Ural Federal University, Ekaterinburg, Russian Federation.*

334. Rapid Dose Titration of Lacosamide: A Randomized, Multicenter, Prospective, Open-Label Study

***Yong-Won Shin, MD**[1], Jangsup Moon, MD, PhD[1], Sang Bin Hong, MD[1], Do-Yong Kim, BSc[1], Hyeyeon Chang, MD[2], Soon-Tae Lee, MD, PhD[1], Keun-Hwa Jung, MD, PhD[1], Kyung-Il Park, MD, PhD[1], Ki-Young Jung, MD, PhD[1], Manho Kim, MD, PhD[1], SeungHwan Lee, MD, PhD[1], Seo Hyun Yoon, PhD[1], Jaeseong Oh, MD, PhD[1], Kyung-Sang Yu, MD, PhD[1], In-Jin Jang, MD, PhD[1], Dong Wook Kim, MD, PhD[3], Yong Won Cho, MD, PhD[4], Kon Chu, MD, PhD[1], Sang Kun Lee, MD, PhD[1]. [1]Seoul National University Hospital, Seoul, Korea, Republic of, [2]Konyang University Hospital, Daejeon, Korea, Republic of, [3]Konkuk University School of Medicine, Seoul, Korea, Republic of, [4]Keimyung University Dongsan Medical Center, Daegu, Korea, Republic of.*

335. Usefulness of Saliva for the Therapeutic Drug Monitoring of Perampanel

*Kon Chu, MD, PhD., **Do-Yong Kim, BS.**, Jangsup Moon, MD, PhD., Yong-Won Shin, MD., Soon-Tae Lee, MD, PhD., Keun-Hwa Jung, MD, PhD., Kyung-Il Park, MD, PhD., Ki-Young Jung, MD, PhD., Manho Kim, MD, PhD., SeoungHwan Lee, MD, PhD., Kyung-Sang Yoo, MD, PhD., In-Jin Jang, MD, PhD., Kaheon Song, BS., Sang Kun Lee, MD, PhD. Seoul National University Hospital, Seoul, Korea, Republic of.*

336. Trends in Oral Anticoagulant Co-Prescription with Valproic Acid among Adults with Epilepsy, 2010-2018

***Emily K. Acton, BS**[1], Scott E. Kasner, MD, MSCE[2], Michael A. Gelfand, MD, PhD[2], Sean Hennessy, PharmD, PhD[1], Sharon X. Xie, PhD[1], John R. Pollard, MD[3], Allison W. Willis, MD, MS[1]. [1]University of Pennsylvania School of Medicine, Philadelphia, PA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]ChristianaCare, Newark, DE, USA.*

337. HLAs Associated with Perampanel-Induced Psychiatric Adverse Effects in a Korean Population

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338. A New Rapid Titration Protocol for Lamotrigine That Reduces the Risk of Skin Rash

***Yoonhyuk Jang, MD. MS.**, Jangsup Moon, MD. PhD., Soon-Tae Lee, MD. PhD., Keun-Hwa Jung, MD. PhD., Kyung-Il Park, MD. PhD., Kon Chu, MD. PhD., Sang Kun Lee, MD. PhD. Seoul National University Hospital, Seoul, Korea, Republic of.*

339. Pharmacokinetic Analysis of Oxcarbazepine and Its Metabolite Mono-Hydroxylated Derivative in Patients with Epilepsy

***Yoonhyuk Jang, MD. MS.**[1], Tae-Joon Kim, MD. MS.[2], Seonghae Yoon, MD. PhD.[3], Jangsup Moon, MD. PhD.[1], Soon-Tae Lee, MD. PhD.[1], Keun-Hwa Jung, MD. PhD.[1], Kyung-Il Park, MD. PhD.[1], Kon Chu, MD. PhD.[1], Sang Kun Lee, MD. PhD.[1]. [1]Seoul National University Hospital, Seoul, Korea, Republic of, [2]Ajou University School of Medicine, Suwon, Korea, Republic of, [3]Seoul National University Bundang Hospital, Bundang, Korea, Republic of.*

340. Perampanel in Patients with a History of Psychiatric Illness: Post Hoc Analysis of Four Randomized Phase III Studies (304, 305, 306, and 335) and Their Open-Label Extensions (307 and 335 OLEx)

***Andres M. Kanner, MD**[1], Anna Patten, PhD[2], Manoj Malhotra, PhD[3]. [1]University of Miami, Miller School of Medicine, Miami, FL, USA, [2]Eisai Ltd., Hatfield, Hertfordshire, United Kingdom, [3]Eisai Inc., Woodcliff Lake, NJ, USA.*

341. Microgrid Recordings from the Human Hippocampal Surface *In Vivo* Reveal Multidirectional Traveling Waves

***Jonathan K. Kleen, MD, PhD**[1], Jason E. Chung, PhD[1], Kristin K. Sellers, PhD[1], Jenny Zhou, B.S.[2], Michael Triplett, B.S.[2], Kye Lee, B.S.[2], Angela Tooker, PhD[2], Razi Haque, PhD[1], Edward Chang, MD[1]. [1]UCSF Medical Center, San Francisco, CA, USA, [2]Lawrence Livermore National Laboratories, Livermore, CA, USA.*

342. Seizure Prevalence in Autoimmune Encephalitis- A Systematic Review

***Arielle Coughlin, BA**, Anusha K. Yeshokumar, MD, Jarrett Fastman, BA, Kendall Psaila, HSD, Michael Harmon, BA, Taylor Randell, BA, Emily Schorr, MD, Helen Han, MD, Hai Hoang, MD, Celine Soudant, MLIS, Nathalie Jette, MD. Icahn School of Medicine at Mount Sinai, New York, NY, USA.*

343. Tranexamic Acid and Post-Operative Seizures: The Glycine Connection

***Catherine A. Kronfol, BA**, Prashant A. Natteru, MD, Hartmut Uschmann, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

344. STAT3 Inhibition Reduces Seizure Frequency and Cognitive Co-Morbidities in a Mouse Model of Temporal Lobe Epilepsy

***Amy R. Brooks-Kayal, MD**[1], Yasmin Cruz Del Angel, M.S.[1], Jessica Carlsen, M.S.[1], Dana Strode, B.S.[1], Kathryn M. Hixson, PhD[2], Allison E. Tipton, B.S.[2], Nicolas Busquet, PhD[1], Michael Mesches, PhD[1], Shelley J. Russek, PhD[2]. [1]University of Colorado, Aurora, CO, USA, [2]Boston University School of Medicine, Boston, MA, USA.*

345. A Prospective, Longitudinal, Observational Study of the Natural History and Functional Status of Patients with Lafora Disease

***Antonio Delgado-Escueta, MD**[1], Viet-Huong Nguyen, PharmD, MPH[1], Alenoush Aramian, PharmD, MPH[1], Jessica Bercow, BS[1], Roberto Michelucci, MD[2], Marcella Broli, MD[3], Maria Tappata, MD[3], Berge Minassian, MD[4], Alison Dolce, MD[4], Souad Messahel, PhD[4], Jose Serratosa, MD, PhD[5], Maria Machio, MD, PhD[5], Beatriz Giraldez, MD[5], JoAnn Flaim, PhD[6], Li Dan, PhD[6], Pulido Robert, PhD[6], Lane Roger, MD, MPH[6], Goldberg Yigal, MD[6], Hal Landy, MD[7]. [1]UCLA - Neurotherapeutics Center, Los Angeles, CA, USA, [2]UCLA - Neurotherapeutics Center, IRCSS-Istituto di Scienze Neurologiche di Bologna, Italy, [3]IRCSS-Istituto di Scienze Neurologiche di Bologna, Bologna, Italy, [4]University of Texas, Southwestern, Dallas, TX, USA, [5]IS Fundación Jimenez Diaz*

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346. Late Perampanel Treatment Stops Severe Midazolam-Refractory Status Epilepticus

Jerome G. Niquet, PhD[1], Ireri G. Franco Estrada, PhD[1], ***Claude G. Wasterlain, MD[2]****. [1]David Geffen School of Medicine at UCLA, Granada Hills, CA, USA, [2]VA Greater Los Angeles Health Care System and David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.*

347. Caregiver Burden in Psychogenic Non-Epileptic Seizures

Ioannis Karakis, MD, PhD, MSc*, Matthew L. Morton, MD, Nicholas J. Janocko, MD, Olivia Groover, MD, Diane L. Teagarden, NP, Hannal K. Villarreal, NP, David W. Loring, PhD, Daniel L. Drane, PhD. Emory University School of Medicine, Atlanta, GA, USA.*

348. A Rare Case of Autonomic Epilepsy

Pretty Sara Idiculla, MBBS*, Sophia Greer, Medical Student, Junaid Habib Siddiqui, MD. Univesity of Missouri, Columbia, MO, USA.*

349. Children and Adolescents with Idiopathic Generalized Epilepsy Treated by AEDs: Changes in Speech Development

Rimma Gamirova, PhD[1,2]*, Elena Gorobets, PhD[1], Tatyana Akhutina, Sc.D[3], Rady Esin, Sc.D[1,2], Regina Gamirova, PhD student[1]. [1]Kazan Federal University, Kazan, Russian Federation, [2]Kazan State Medical Academy, Kazan, Russian Federation, [3]Moscow State University, Moscow, Russian Federation.*

350. The Effect of Human Herpes Virus 6 on Hippocampal Volumes in Temporal Lobe Epilepsy

Elizabeth Akinsoji, BA, Emily Leibovitch, PhD, Jeanne Billioux, MD, Osorio Lopes Abath Neto, MD, Abhik Ray-Chaudhury, MD, Sara Inati, MD, Kareem Zaghloul, MD PhD, John Heiss, MD PhD, Steven Jacobson, PhD, ***William Theodore, MD****. NIH, Bethesda, MD, USA.*

351. The Referential Montage Poorly Localizes Cortico-Cortical Evoked Potentials

Adam Dickey, MD, PhD*, Abdulrahman Alwaki, MD, Ammar Kheder, MD, MRCP, Robert Gross, MD, PhD, Jon Willie, MD, PhD, Daniel Drane, PhD, Nigel Pedersen, MBBS. Emory Univeristy, Atlanta, GA, USA.*

352. An Approach to the Analysis and Successful Treatment of Epilepsy Due to Periventricular Nodular Heterotopia - Corticocortical Evoked Potentials, Signal Processing and Radiofrequency Ablation

Veeresh Kumar N. Shivamurthy, MD*, Adam S. Dickey, MD, Harshad S. Ladha, MD, Jon T. Willie, MD, PhD, Ammar Kheder, M.D., MRCP, Nigel P. Pedersen, MD. Emory University School of Medicine, Atlanta, GA, USA.*

353. Status Epilepticus as an Extreme Presentation of Dialysis Disequilibrium Syndrome

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354. Near-Fainting with Swallowing: Two Cases of Swallow Syncope

Chindo B. Mallum, MD[1]*, Roohi Katyal, MD[1], Maria Shoaib, MD[1], Rajesh Sharma, MD[2]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, [2]Veteran's Affairs Medical Center, Oklahoma City, OK, USA.*

355. Voltage-Based Algorithmic Detection of Postictal Generalized Electroencephalographic Suppression

L. Brian Hickman, MD, MSCI[1,2]*, Robert E. Hogan, MD[3], Alyssa Labonte, BS[3], Courtney W. Chan, BA[3], Emma R. Huels, BS[4], Mohammad Mehdi Kafashan, PhD[3], ShiNung Ching, PhD[3], Eric J. Lenze, MD[3], Luigi Maccotta, MD, PhD[3], Lawrence N. Eisenman, MD, PhD[3], Nuri B. Farber, MD[3], Michael S. Avidan, MBBCh[3], Ben J. A. Palanca, MD, PhD, MSc[3]. [1]University of California, Los Angeles, Los Angeles, CA, USA, [2]University of California, Irvine, Irvine, CA, USA, [3]Washington University in St. Louis, St. Louis, MO, USA, [4]University of Michigan, Ann Arbor, MI, USA.*

356. Non-Convulsive Seizure as Initial Manifestation of Posterior Reversible Encephalopathy Syndrome (PRES)

Madiha Tariq, MD*, Ruiqing Sun, MD, Todd Masel, MD. UTMB, Galveston, TX, USA.*

357. A Case Report of Mesial Temporal Lobe Epilepsy Misdiagnosed as Cyclic Vomiting Syndrome

Michael M. Chang, D.O*, Kiran M. Kanth, M.D, Kevin J. Keenan, M.D, Mustafa K. Ansari, M.D, Meghan M. Branston, D.O, Beatrice S. Akers, D.O, Lue Lao, M.D. UC Davis Medical Center, Sacramento, CA, USA.*

358. Risk Factors Associated with Hyperammonemia Following Unprovoked Convulsive Seizures - Systematic Literature Review

Nurose Karim, MD*, Giana Dawod, BA, Nicholas Henkel, BS, Imran Ali, MD, Ajaz Sheikh, MD. University of Toledo COM LS, Toledo, OH, USA.*

359. Clinical, Radiographic, and Electroencephalographic Findings of Seizures Associated with Stroke: A Retrospective Study

Sidra Saleem, MD*, Nurose Karim, MD, Maria Rabbani, MD, Anum Riaz, MD, Imran I. Ali, MD, Ajaz Sheikh, MD. University of Toledo COM LS, Toledo, OH, USA.*

K-587. Prehospital Midazolam Use and Outcomes among Patients with Out-of-Hospital Status Epilepticus

Elan L. Guterman, MD[1], *Joseph K. Sanford, MD*[1], *John P. Betjemann, MD*[2], *Li Zhang, PhD*[1], *James F. Burke, MD*[3], *Daniel H. Lowenstein, MD*[1], *S. Andrew Josephson, MD*[1], *Karl A. Sporer, MD*[1]. [1]*University of California San Francisco, San Francisco, CA, USA,* [2]*Kaiser Permanente, San Francisco Medical Center, San Francisco, CA, USA,* [3]*University of Michigan, Ann Arbor, MI, USA.*

K-589. Epileptic Encephalopathy in Kcna1 KO Mice Disrupts Active State Organization

John Bass, Master of Science, Catharina Schirmer, Bachelors in Animal Science, Miranda Jankovic, Bachelor of Science, Paarth Kapadia, Bachelor of Science, ***Vaishnav Krishnan, MDPhD****. Baylor College of Medicine, Houston, TX, USA.*

K-599. Models and Mechanisms of DEPDC5-Related Epilepsies

Tao Yang, PHD, Hsin-Yi Kao, PHD, Shuntong Hu, MD, PHD, Wei-Chih Chang, PHD, Temenuzhka Mihaylova, MD, PHD, Brendon Watson, MD, PHD, ***Yu Wang, MD, PHD****. University of Michigan, Ann Arbor, MI, USA.*

K-601. Repetitive Transcranial Magnetic Stimulation to Assess Cortical Plasticity & Suppress Spikes in Pediatric Epilepsy

Fiona Baumer, MD*. Stanford University, Stanford, CA, USA.*

Neuromuscular Disease

360. Neuropathy-Causing TRPV4 Mutations Disrupt TRPV4-RhoA Interactions and Impair Cytoskeletal Regulation

Brett A. McCray, MD, PhD[1], *Erika Diehl, B.S.*[2], *Jeremy M. Sullivan, PhD*[1], *William H. Aisenberg, B.S.*[1], *Alexander R. Lau, B.S.*[1], *Dominick J. Rich, B.S.*[1], *Ute A. Hellmich, PhD*[2], *Thomas E. Lloyd, MD, PhD*[1], *Charlotte J. Sumner, MD*[1]. [1]*Johns Hopkins School of Medicine, Baltimore, MD, USA,* [2]*Johannes Gutenberg-Universität Mainz, Mainz, Germany.*

361. Myasthenia Gravis: From Early Descriptions to Early Treatments

J. David Avila, MD*. Geisinger Medical Center, Danville, PA, USA.*

362. Chemically Patterned Hydrogel Scaffolds Provide Cell-Assembled Matrices to Guide Spinal Cord Regeneration

Ahad M. Siddiqui, PhD[1], *Rosa Brunner, MD*[2], *Weiss Georgina, BS*[2], *Rachel Stewart, MS*[3], *Simone Pinsker, MD*[2], *Tammy Strickland, MS*[3], *Bingkun Chen, MD, PhD*[1], *Kelly Lim, BS*[4], *Gregory M. Harris, PhD*[4], *Alan L. Miller, PhD*[1], *Brian E. Waletzki, BS*[1], *Jodi Silvernail, BS*[1], *Jarred Nesbitt, BS*[1], *Schwartz Jeffery, PhD*[4], *Jean E. Schwarzbauer, PhD*[4], *Michael J. Yaszemski, MD, PhD*[1], *Anthony J. Windebank, MD*[1], ***Nicolas Madigan, MB BCh BAO, PhD***[1]. [1]*Mayo Clinic, Rochester, MN, USA,* [2]*Paracelsus Medical University, Salzburg, Austria,* [3]*National University of Ireland, Galway, Ireland,* [4]*Princeton University, Princeton, NJ, USA.*

363. Pediatric Small-Fiber Neuropathy: Presentations, Causes, Outcomes

Madeleine C. Klein, BS*, Khosro Farhad, MD, David C. Dredge, MD, Heather M. Downs, BS, Max M. Klein, PhD, William S. David, MD, PhD, Anne Louise Oaklander, MD, PhD. Massachusetts General Hospital, Boston, MA, USA.*

364. Brain Strength: Multi-Modal Brain MRI Predicts Grip Strength

Kenneth A. Weber, DC, PhD[1]*, Tor D. Wager, PhD*[2], *Pranav A. Upadhyayula, BS*[1], *Christine S. Law, PhD*[1], *Yoni K. Ashar, PhD*[1], *Nitin K. Prabhakar, MD*[1], *Simiao Zhu, BS*[1], *Gadi Gilam, PhD*[1], *Suchandrima Banerjee, PhD*[3], *Scott L. Delp, PhD*[1], *Gary H. Glover, PhD*[1], *Trevor J. Hastie, PhD*[1], *Sean Mackey, MD, PhD*[1]. [1]*Stanford University, Palo Alto, CA, USA,* [2]*Darmouth University, Hanover, NH, USA,* [3]*GE Healthcare, Menlo Park, CA, USA.*

365. Using Active Digital Phenotyping to Quantify Function and Cognition in Amyotrophic Lateral Sclerosis

Sheena Chew, MD[1]*, Ella Collins, BS*[1], *Katherine Burke, DPT*[1], *Syed Minhaj Rahman, BS*[1], *Josh Cosman, PhD*[2], *Tairmae Kangarloo, BS*[2], *Krzysztof Z. Gajos, PhD*[3], *Anoopum Gupta, MD*[1], *James Berry, MD, MPH*[1]. [1]*Massachusetts General Hospital, Boston, MA, USA,* [2]*Biogen, Inc., Cambridge, MA, USA,* [3]*Harvard University, Cambridge, MA, USA.*

366. *DNAJB6* Isoform Switching: Mechanistic Insights and Therapeutic Potential for Limb Girdle Muscular Dystrophy 1D

Andrew R. Findlay, MD*, May Paing, PhD, Jil Daw, BS, Sara Pittman, BS, Rocio Bengoechea, PhD, Conrad C. Weihl, MD, PhD. Washington University St. Louis School of Medicine, Saint Louis, MO, USA.*

367. When a Neuropathy Doesn't Rhyme, it Could be POEMS Syndrome

Bernice Anderson, BS*, Krish Khandelwal, MBBS, Prashant Natteru, MD, Saurabh Shukla, MD, Amanda Witt, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

368. Futility of Intravenous Immunoglobulins in a Subset of Lower Motor Neuron Syndromes

Bernice Anderson, BS*, Krishnakant Khandelwal, MBBS, Prashant Natteru, MD, Saurabh Shukla, MD, Amanda Witt, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

369. Longitudinal Study of Cognitive and Behavioral Impairments in the Veteran ALS Population

Charley Jang, B.S.[1], *Nicholas J. Jackson, PhD*[1], *Nasheed I. Jamal, M.D.*[2,1]. [1]*David Geffen School of Medicine at UCLA, Los Angeles, CA, USA,* [2]*VA GLA Healthcare System, Los Angeles, CA, USA.*

370. Characterizing the Histological and Behavioral Phenotypes of a Humanized Knock-In Mouse Modeling a Deep Intronic Mutation in Collagen VI-Related Dystrophy

Fady Guirguis, B.S.[1], *Véronique Bolduc, Ph.D.*[2], *Jun Cheng, Ph.D.*[3], *Lisa Garrett, Ph.D.*[3], *Carsten G. Bönnemann, Ph.D.*[2]. [1]*Neuromuscular and Neurogenetic Disorders of Childhood Section, NINDS, NIH Medical Research Scholars Program, NIH, Bethesda, MD, USA,* [2]*Neuromuscular and Neurogenetic Disorders of Childhood Section, NINDS, NIH, Bethesda, MD, USA,* [3]*Embryonic Stem Cell and Transgenic Mouse Core, NHGRI, NIH, Bethesda, MD, USA.*

371. Heat Sensitivity in Lou Gehrig's Disease

Madhusudan Patel, MD[1], ***Karla Licona, MPH***[2], *Alan R. Hirsch, MD*[1]. [1]*Smell & Taste Treatment & Research Foundation, Chicago, IL, USA,* [2]*All Saints University School of Medicine, Roseau, Dominica.*

372. Dietary Weight Loss May Halt Progression of Polyneuropathy in Patients with Obesity

Brian Callaghan, MD, MS*, Gulcin Akinci, MD, Evan Reynolds, PhD, Mousumi Banerjee, PhD, Eva L. Feldman, MD, PhD. University of Michigan, Ann Arbor, MI, USA.*

373. Home-Based Teleyoga Breathing Meditation in Patients with ALS

Jinny O. Tavee, MD[1], *Pia Sanpitak, BS*[2], *Senda Ajroud Driss, MD*[3], *John M. Coleman, MD*[3], *Lisa Wolfe, MD*[3]. [1]*Northwestern Feinberg School of Medicine, Chicago, IL, USA,* [2]*Northwestern University, Chicago, IL, USA,* [3]*Northwestern University Feinberg School of Medicine, Chicago, IL, USA.*

374. Overview of the Healey Center's Expanded Access Programs for Investigational Treatments in Amyotrophic Lateral Sclerosis

Megan Yerton, AB*, Sarah Luppino, RN, Margot Rohrer, RN, Taylor Stirrat, RN, Margaret Bruno, RN, Judith R. Carey, RN, Cassandra Lieberman, BA, Dario Gelevski, BS, Michael Doyle, BA, Neil Parikh, BA, Alexander Sherman, PHD, MS, Ervin Sinani, B.S., Derek D'Agostino, BA, Hong Yu, MS, Jennifer Scalia, MSN, AGNP-C, Darlene Sawicki, MSN, NP-BC, Suma Babu, MPH, MBBS, Sheena Chew, MD, Katharine Nicholson, MD, Sabrina Paganoni, MD, James D. Berry, MD, Merit E. Cudkowicz, MD. Healey Center for ALS and Massachusetts General Hospital, Boston, MA, USA.*

375. Rationale and Design of Neuro-Ttransform, a Phase 3 Study to Evaluate the Efficacy and Safety of AKCEA-TTR-LRx (ion-682884) in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy (hATTR-PN)

Sami Khella, MD[1], *Morie A. Gertz, M.D., M.A.C.P*[2], *John L. Berk, M.D.*[3], *Li-Jung Tai, MD, PhD*[4], *Nicholas J. Viney, BSc.*[5], *Cecilia Monteiro, MD, PhD*[5], *Gustavo Buchele, M.D., PhD*[5], *Michela Brambatti, M.D., MSC*[5], *Sotirios Tsimikas, MD, FACC, FAHA, FSCAI*[5], *Shiangtung W. Jung, PhD*[5], *Louis St. L. O'Dea, MB B.Ch,. BAO, FRCP(C)*[6], *Eugene Schneider, MD*[5], *Richard S. Geary, PhD*[7], *Brett P. Monia, PhD*[5]. [1]*University of Pennsylvania School of Medicine, Philadelphia, PA, USA,* [2]*Mayo Clinic, Rochester, MN, USA,* [3]*Boston University - School of Medicine, Boston, MA, USA,* [4]*Ionis Pharmaceuticals, Inc, Carlsbad, CA, USA,* [5]*Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA,* [6]*Akcea Therapeutics, Philadelphia, PA, USA,* [7]*Ionis Pharmaceuticals. Inc., Carlsbad, CA, USA.*

376. Historical Perspective of Lambert Eaton and Rooke, Myasthenic Syndrome

Shri Kant Mishra, M.D., M.S., ABMS, FAAN, FNAA, FANA[1], *Shaweta Khosa, M.B.B.S.*[1], *Bhavesh Trikamji, MD*[2]. [1]*Olive View–UCLA Medical Center, Sylmar, CA, USA,* [2]*Washington University in St Louis, St Louis, MO, USA.*

377. Myotonic Dystrophy Phenocopies Sleep Features of Idiopathic Hypersomnia

Zachary Y. Chen, BS*, Lynn M. Trotti, MD, MSc, David B. Rye, MD, PhD. Emory University, Atlanta, GA, USA.*

378. Humoral Immune Endoneurial Microvasculopathy: Treatable Non-Inflammatory Axonal Neuropathies

Bhavesh Trikamji, MD*, Alan Pestronk, MD. Washington University in St Louis, St Louis, MO, USA.*

379. Myositis Associated Anti-NT5C1A Autoantibody in Clinical Practice

Chiseko Ikenaga, MD, PhD[1], *Andrew R. Findlay, MD*[1], *Namita A. Goyal, MD*[2], *Sarah Robinson, MS*[1], *Jonathan Cauchi, MD*[2], *Yessar Hussain, MD*[3], *Leo H. Wang, MD, PhD*[4], *Joshua C. Kershen, MD*[5], *Brent A. Beson, MD*[5], *Michael Wallendorf, PhD*[1], *Robert C. Bucelli, MD, PhD*[1], *Tahseen Mozaffar, MD*[2], *Alan Pestronk, MD*[1], *Conrad C. Weihl, MD, PhD*[1]. [1]*Washington University in St. Louis, St. Louis, MO, USA,* [2]*University of California, Irvine, CA, USA,* [3]*Austin Neuromuscular Center, The University of Texas Dell Medical School, Austin, TX, USA,* [4]*University of Washington, Seattle, WA, USA,* [5]*Integris Southwest Medical Center, Oklahoma City, OK, USA.*

380. Accurate Test of Limb Isometric Strength (ATLIS) as an Outcome Measure in Upper Motor Neuron Predominant ALS and Primary Lateral Sclerosis

Frank Diaz, M.D., Ph.D.[1], *Peggy Allred, PT, DPT*[2], *Carolyn Prina, BS*[1], *Koral Wheeler, MS*[3], *Dana Fine, BS, CCRP*[1],

Jillian Doherty, BS[1], Viviana Valencia, BS[1], Robert H. Baloh, M.D., Ph.D.[1]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, USA, [2]AveXis, San Diego, CA, USA, [3]University of Southern California, Los Angeles, CA, USA.

381. Electrical Myotonia in Diagnosis and Monitoring of Immune-Mediated Necrotizing Myopathy

James D. Triplett, B.Med, M.Med[1], *Shahar Shelly, MD[1], Guy Livne, Bachelor Science[2], Margherita Milone, MD, PhD[1], Charles D. Kassardjian, MD[3], Teerin Liewluck, MD[1], Cecilia Kelly, MD[1], Elie Naddaf, MD[1], Ruple Laughlin, MD[1], Divanshu Dubey, MBBS[1], John Mills, PhD[4], Jay Mandrekar, PhD[5], Christorpher Klein, MD[1]. [1]Department of Neurology, Mayo Clinic, Rochester, Rochester, MN, USA, [2]guylivne.com, Rochester, MN, USA, [3]Division of Neurology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada, [4]Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Rochester, MN, USA, [5]Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Rochester, MN, USA.*

383. A Unique Presentation of Severe Dysautonomia in Guillain Barre' Syndrome (GBS)

Azima Shaji, M.D*, Divisha Raheja, M.D, Michel Ritenuti, D.O. St. Luke's University and Health Network, Easton, PA, USA.*

384. A Unique Case of Progressive Spasticity and Profound Brain Atrophy in a Young Female

Catherine Craven, MD*, Naaima Mufti, MD, Divisha Raheja, MD. St. Luke's University Health Network, Bethlehem, PA, USA.*

385. Dual CASPR2 and LGI1 Antibody-Mediated Guillain-Barré Syndrome Associated with Severe Neuropathic Pain, Muscle Membrane Hyperexcitability, and Radiographic Evidence of Renal Cell Cancer

Elizabeth Isaacoff, MD, MBE*, Waqar Waheed, MD. University of Vermont Medical Center, Burlington, VT, USA.*

386. An Unusual Case of Acute Flaccid Paralysis Associated with West Nile Virus Involving Paraspinal and Bulbar Muscles

Hadi Mohammad Khanli, MD[1], *Lynn Kataria, MD[2], Marshall Balish, MD[2], Ping Zhai, MD[2]. [1]George Washington University, Washington, DC, USA, [2]Washington DC VA Medical Center, Washington, DC, USA.*

387. Hu-Dat? A Case of Paraneoplastic Sensory Neuronopathy and Cerebellitis

Maryam Zulfiqar, MD*, Prashant Natteru, MD, Candise Johnson, MS, Krishnakant Khandelwal, MD, Saurabh Shukla, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

388. Droopy Eyelids: Think Beyond the Conventional Paradigm!

Prashant A. Natteru, MD*, Chandra Sekhar Mannyam, MD, Saurabh Shukla, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

389. Neurotypical Control Testing of an 8-Channel BCI Speller

Ravi Rajmohan, MD, PhD*, An Do, MD. University of California-Irvine, Orange, CA, USA.*

390. Recurrent Malignant Thymoma in Refractory Myasthenia Gravis

Yousaf Ajam, MD*, Mert Erdenizmenli, BS, Naushin Jazebi, MD, Xiang Fang, M.D., Ph.D., FAAN, FANA. University of Texas Medical Branch, Galveston, TX, USA.*

391. Machine Learning Optimized Dynamic Meta-Analysis to Assess and Predict the Multifactorial Nature of Amyotrophic Lateral Sclerosis

Eleanor Ridgeway, B.S.*, Albert Lee, B.S., Sakshi Deshpande, B.S., Ahad Khatri, B.S., Cassie S. Mitchell, Ph.D. Georgia Institute of Technology, Atlanta, GA, USA.*

K-598. Macrophage-Derived Vascular Endothelial Growth Factor-A is Integral to Neuromuscular Junction Reinnervation after Nerve Injury

Chueing-Yi Lu, MD, MS, Katherine Santosa, MD, MS, Albina Jablonka-Shariff, PhD, Bianca Vannucci, MD, Anja Fuchs, PhD, Isaiah Turnbull, MD, PhD, Deng Pan, BS, Matthew Wood, PhD, ***Alison Snyder-Warwick, MD****. Washington University, St Louis, MO, USA.*

Thursday Poster Presentations

Autoimmune Neurology

392. A Rare Case of Recurrent Unilateral Facial Nerve Paralysis in a Patient with Neurosyphilis

Alok Dabi, M.D.*, Neeharika Thottempudi, M.D. University of Texas Medical Branch, Galveston, TX, USA.*

393. A Rare Case of Miller Fisher Syndrome in Patient with History of Guillain-Barre Syndrome

Alok Dabi, MBBS, MD*, Lalitha Battineni, MD. Unviersity of Texas Medical Branch, Galveston, TX, USA.*

394. A Retrospective, Cross-Sectional Study Evaluating Plasma Neurofilament Light Levels in Autoimmune Encephalitis

Amanda L. Piquet, MD*, Enrique Alvarez, MD, PhD, Jeffrey L. Bennett, MD, Courtney` Knapp, BSN, RN, Stefan Sillau,*

PhD, Christopher Mizenko, MS, Kavita Nair, PhD, Timothy Vollmer, MD. University of Colorado, Aurora, CO, USA.

395. Autoimmune Dysautonomia and Ataxia Due to Ganglionic Acetylcholine Receptor Autoantibodies

***Duarte Machado, MD**, Alison Carlson, APRN. Hartford Healthcare, Hartford, CT, USA.*

396. Partial Stiff Person Syndrome as a Stroke Mimic

***Duarte Machado, MD**, Kendall Hodges, APRN. Hartford Healthcare, Hartford, CT, USA.*

397. Neuronal Uptake, Antibody Binding, and Injury by Anti-Ma2 Antibodies in Organotypic Rat Brain Cultures: A Possible Direct Role for Paraneoplastic Autoantibody in Disease Pathogenesis

***Jonathan Galli, MD**[1,2], Noel G. Carlson, PhD[1,2], John E. Greenlee, MD[1,2]. [1]VA SLC HCS, Salt Lake City, UT, USA, [2]University of Utah School of Medicine, Salt Lake City, UT, USA.*

398. Magnetic Resonance Imaging Findings in *Cryptococcus Neoformans* Meningoencephalitis and Its Association with Clinical Outcomes

***Kon Chu, Md PhD**, Sang Kun Lee, Md PhD, Woo-Jin Lee, MD. Seoul National University Hospital, Seoul, Korea, Republic of.*

399. Debilitating Human Herpesvirus 6 Myelitis (HHV-6) in an Immunocompetent Patient — Case Presentation and Literature Review

*Wenyang Li, MD, Karl Echiverri, MD, **Mam Ibraheem, MD, MPH**. University of Kentucky-Department of Neurology, Lexington, KY, USA.*

400. Probable Autoimmune Encephalitis without Detected Autoantibody: Clinical Characteristics and Treatment Response

*Kon Chu, Md PhD, **Woo-Jin Lee, MD**, Soon-Tae Lee, Md PhD, Keun-Hwa Jung, Md PhD, Kyung-Il Park, Md PhD, Sang Kun Lee, Md PhD. Seoul National University Hospital, Seoul, Korea, Republic of.*

401. Beyond the IgG4 Antibody Subclass in Musk Myasthenia Gravis: Novel Evidence for the Pathogenicity of IgG1,2 and 3

***Michelangelo Cao, MD, PhD**, Judith Cossins, DPhil, Weiwei Liu, PhD, Susan Maxwell, MSC, Richard Webster, PhD, David Beeson, PhD, Angela Vincent, MD FRCPath FRS. University of Oxford, Oxford, United Kingdom.*

402. Factors Associated with Exercise Participation in People with Multiple Sclerosis

***Lindsey Wooliscroft, M.D., M.S.**[1], Carin Waslo, B.S., M.S.[2], Grace Clark, B.A.[1], Angela Senders, N.D., M.C.R.[1], Elizabeth Silbermann, M.D.[1], Anna Orban, B.Sc.[1], Jessica Rice, M.D.[1], Vijayshree Yadav, M.D., M.C.R.[1], Rebecca Spain, M.D., M.S.P.H.[2], Michelle Cameron, M.D., P.T., M.C.R.[2]. [1]Oregon Health & Science Unviersity, Portland, OR, USA, [2]VA Portland Health Care System, Portland, OR, USA.*

403. Blepharospasm: Expanding the MOG Spectrum or Incidental Finding

***Hannah W. Austin, BS**[1], Mary A. Willis, MD[2]. [1]University of Mississippi Medical Center, Jackson, MS, USA, [2]Department of Neurology, University of Mississippi Medical Center, Jackson, MS, USA.*

404. Natural Language Processing Analyses of Written Text across Stages of Illness in Anti-NMDA Receptor Encephalitis

***Kelsey Martin, BA**[1], Sahil Garg, PhD[1], Guillermo Cecchi, PhD[2], Cheryl Corcoran, MD[1], Anusha Yeshokumar, MD[1]. [1]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]IBM Corporation, New York, NY, USA.*

405. Guillain-Barre Syndrome after Platinum-Based Chemotherapy

***Maria J. Abraham, B.S.**, Yousaf Ajam, M.D., Elena Shanina, MD, PhD. University of Texas Medical Branch at Galveston, Galveston, TX, USA.*

406. Hashimoto Encephalopathy

***Tamari Papidze, MD, June 2020**, Alexandre Tsereteli, MD, Nika Karazanashvili, MD in June 2020. American MD program of Emory University, Tbilisi, Georgia.*

407. Rapidly Progressive Neuromyelitis Optica Spectrum Disorder

***Tamer G. Ghanayem, BA**[1], Varun Shah, MD[2], Xiang Fang, MD[2], Elena Shanina, MD[2]. [1]University of Texas Medical Branch, School of Medicine, Galveston, TX, USA, [2]University of Texas Medical Branch, Department of Neurology, Galveston, TX, USA.*

408. $Ca_V\alpha 2\delta$ Autoimmune Encephalitis: A Novel Antibody and Its Characteristics

***Soon-Tae Lee, MD, PhD**, Byung Ju Lee, PhD, Ji-Yeon Lee, MS, Konc Chu, MD, PhD, Sang Kun Lee, MD, PhD, Won-Kyung Ho, MD, PhD. Seoul National University Hospital, Seoul, Korea, Republic of.*

409. Genetics of Anti-NMDAR Encephalitis Implicates Natural Killer Cells

Aditya Ambati, PhD[1], *Ling Lin, MD PhD*[1], *Sergio Muniz-Castrillo, PhD*[2], *AM Pinto, PhD*[2], *Hanna Ollila, PhD*[1], *Veronique Rogemond, PhD*[2], *- NMDAR-Ab working group, MD PhD*[1], *Carsten Finke, MD PhD*[3], *Frank Leypoldt, MD PhD*[4], *Maarten Titulaer, MD PhD*[5], *Jérôme Honnorat, MD PhD*[2], *Emmanuel Mignot, MD PhD*[1]. [1]*Stanford, Palo Alto, CA, USA,* [2]*French Reference Center on Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis, Hospices Civils de Lyon, Hôpital Neurologique, 59 Boulevard Pinel, 69677, Bron cedex, France,* [3]*Department of Neurology with Experimental Neurology , Charité Universitätsmedizin, Berlin, Germany,* [4]*Institute of Clinical Chemistry, Kiel University, Kiel, Germany,* [5]*Erasmus University Medical Center, Rotterdam, Netherlands.*

410. Optical Coherence Tomography Demonstrates Occult Optic Neuropathy in Neurosarcoidosis

Andrea Salazar-Camelo, MD*, Olwen C. Murphy, MBBCh, Angeliki Filippatou, MD, Jeffrey Lambe, MD, Peter A. Calabresi, MD, Shiv Saidha, MBBCh, Carlos A. Pardo-Villamizar, MD. Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA.*

411. Longitudinal Analysis of Cortical Demyelination in Multiple Sclerosis (MS) Using Multimodal High-Resolution 7T MRI

Erin S. Beck, MD, PhD[1], *Josefina Maranzano, MD, PhD*[2,3], *Pascal Sati, PhD*[1], *Stefano Filippini, MD*[1,4], *Mark Morrison, BA*[1], *Nicholas J. Luciano, BA*[1], *Daniel J. Suto, BA*[1], *Irene Cortese, MD*[1], *Sridar Narayanan, PhD*[2], *Daniel S. Reich, MD, PhD*[1]. [1]*National Institutes of Health, Bethesda, MD, USA,* [2]*Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada,* [3]*University of Quebec in Trois-Rivieres, Trois-Rivieres, QC, Canada,* [4]*University of Florence, Florence, Italy.*

412. Autoimmunity to Hypocretin/Orexin and Molecular Mimicry to Flu in Type 1 Narcolepsy

Guo Luo, PhD[1], *Aditya Ambati, PhD*[1], *Ling Lin, PhD*[1], *Markku Partinen, PhD*[2], *Xuhuai Ji, PhD*[1], *Holden Maecker, PhD*[1], *Emmanuel Mignot, PhD*[1]. [1]*Stanford University, Palo Alto, CA, USA,* [2]*University of Helsinki, Helsinki, Finland.*

413. Improving Accuracy of Myasthenia Gravis Autoantibody Testing by Reflex Algorithm

Shahar Shelly, MD*, Pritikanta Paul, MD, Hongyan Bi, MD, Divyanshu Dubey, MD, Margherita Milone, MD, Eric J. Sorenson, MD, Brian A. Crum, MD, Ruple S. Laughlin, MD, Teerin Liewluck, MD, Jay Mandrekar, MD, Sean J. Pittock, MD, Anastasia Zekeridou, MD,PhD, Andrew McKeon, MD, Charles (Michel) M. Harper, MD, John R. Mills, PhD, Christopher J. Klein, MD. Mayo Clinic, Rochester, MN, USA.*

414. A Rare Case of Antisynthetase Syndrome Associated Immune Mediated Myopathy in an Adult Male

Shaweta Khosa, M.B.B.S.[1], *Shri Kant Mishra, M.D.*[1], *James Dompor, M.D.*[2]. [1]*Olive View–UCLA Medical Center, Sylmar, CA, USA,* [2]*University of California, Los Angeles, Los Angeles, CA, USA.*

415. Longitudinally Extensive Transverse Myelitis: A Rare Neuromyelitis Optica Spectrum Disorder

Aman Deep, MD*, Andrew N. Wilner, MD. University of Tennessee Health Science Center Neurology, Memphis, TN, USA.*

416. Neuronal Septin Autoimmunity: Differentiated Serological Profiles & Clinical Findings

Cecilia Zivelonghi, MD[1], *Josephe A. Honorat, MD, PhD*[1], *Ramona Miske, PhD*[2], *Madeleine Scharf, PhD*[2], *Shannon R. Hinson, PhD*[1], *Jacquelyn Grell, MS*[1], *Robert C. Bucelli, MD, PhD*[3], *Adrian Budhram, MD*[1], *Louis Caplan, MD*[4], *Ellie Choi, MD*[5], *Marc H. Levin, MD, PhD*[6], *Merati Melody, DO*[7], *Maria Nagel, MD*[8], *Muhammad Taher Al-Lozi, MD*[9], *Vanda Lennon, MD, PhD*[1], *Sean Pittock, MD*[1], *Andrew McKeon, MD*[1]. [1]*Mayo Clinic, Rochester, MN, USA,* [2]*Euroimmun, Luebeck, Germany,* [3]*Washington University, St Louis, MO, USA,* [4]*Beth Israel Deaconess Medical Center, Boston, MA, USA,* [5]*Overlake Hospital, Bellevue, WA, USA,* [6]*Palo Alto Medical Foundation, Palo Alto, CA, USA,* [7]*Michigan State University, Lansing, MI, USA,* [8]*University of Colorado, Aurora, CO, USA,* [9]*University of Washington, St Louis, MO, USA.*

417. Rare Case of Immunotherapy Refractory Fatal Neuromyelitis Optica Syndrome Related Encephalitis

Alok Dabi, MD, Lalitha Battineni, MD, ***Diaa Hamouda, MD****. University of Texas Medical Branch, Galveston, TX, USA.*

418. Assessing Diagnostic Accuracy of Multiple Sclerosis: A Quantitative Survey of Neurology Residents at an Academic Institution

Fred O. Odago, MD*, Joshua Chalkley, DO, Padmaja Sudhakar, MD. University of Kentucky, Lexington, KY, USA.*

419. Anti-Amphiphysin Positive Partial Stiff Person Syndrome in an Elderly Woman with a Breast Mass

Hibatullah Abu El-Haija, MD*, Bhanu Gogia, MD, Elena Shanina, MD, Jing He, MD, Xiang Fang, MD, PhD, FAAN, FANA, Xiangping Li, MD, MPA. UTMB, Galveston, TX, USA.*

420. Covid-19 Presenting as Post-Infectious Myelitis: A Case Report

Masaki Nagamine, MD*, Sahar Osman, MD, Nita Chen, MD, Yama Akbari, MD, Lilit Mnatsakanya, MD, Manisha Korb, MD, Tahseen Mozaffar, MD. University of California Irvine, Anaheim, CA, USA.*

421. Pembrolizumab-Induced Myositis and Encephalitis with Bi-Thalamic Involvement Responsive to Rituximab

***Matthew K. Techy, MD**, Sunandana Chandra, MD, Minjee Kim, MD, Jinny Tavee, MD. Northwestern University, Chicago, IL, USA.*

422. A Rare Case of Miller Fisher Syndrome Presenting with Hypoglossal Nerve Palsy

***Neeharika Thottempudi, MD**, Diaa Hamouda, MD, Bhanu Gogia, MD, Laura J. Wu, MD. University of Texas Medical Branch, Galveston, TX, USA.*

423. Behcet's Disease Presenting with Intracranial Hypertension Secondary to Superior Vena Cava Thrombosis Successfully Treated with Thrombectomy

***Payam Sadry, DO**, Maahum Ahmed, BS, Jennifer Amsdell, MD, Talal Derani, MD, Ajaz Sheikh, MD. University of Toledo, Toledo, OH, USA.*

424. Uncommon Manifestations of Latent HHV-6: An Unusual Case of Acute Onset Dysarthria and Diplopia

***Payam Sadry, DO**, Maahum Ahmed, BS, Ajaz Sheikh, MD, Talal Derani, MD. University of Toledo, Toledo, OH, USA.*

425. Occult Growing Teratoma as the Cause of Protracted Symptoms in an Anti-NMDA Receptor Encephalitis Patient with Prior Ovarian Teratoma Removal: Implications for Long-Term, Repeated Monitoring and Treatment

***Sang Bin Hong, MD**, Yong-Won Shin, MD, Soon-Tae Lee, MD, PhD, Sang Kun Lee, MD, PhD, Kon Chu, MD, PhD. Seoul National University Hospital, Seoul, Korea, Republic of.*

426. Cerebrospinal Fluid Oligoclonal Bands in Anti-NMDA Receptor Encephalitis

***Sang Bin Hong, MD**, Yong-Won Shin, MD, Jangsup Moon, MD, PhD, Woo-Jin Lee, MD, Kon Chu, MD, PhD, Sang Kun Lee, MD, PhD. Seoul National University Hospital, Seoul, Korea, Republic of.*

427. Subacute Encephalopathy and New-Onset Seizures in Autoimmune CASPR2-Antibody Encephalitis with Phenotypical Similarities to Creutzfeldt-Jakob Disease

***Tian Wang, MD**, Amy Safadi, MD, Nathan Bicher, MD, Gholam Motamedi, MD, Benjamin Osborne, MD. Department of Neurology, Georgetown University Hospital, Washington, DC, USA.*

428. Anti-Myelin Oligodendrocyte Glycoprotein (MOG) Antibody-Associated Bilateral Optic Neuritis: To Treat or Not to Treat?

***Yousaf Ajam, MD**, Xiangping Li, MD. University of Texas Medical Branch, Galveston, TX, USA.*

K-578. Effects Of Myocyte Enhancer Factor 2c (mef2c) On Microglia Function

*Emily Hansen, BA, MS[1,2], Zahara Keulen, BS, MS[3], Shreya Shriram, .[1], Samuel Anavim, .[1], Anna Warden, PhD[1,2], Claudia Z. Han, PhD[1], Christopher K. Glass, MD PhD[1], **Nicole G. Coufal, MD PhD**[1,2]. [1]University of California, San Diego, La Jolla, CA, USA, [2]Sanford Consortium for Regenerative Medicine, La Jolla, CA, USA, [3]University of California, Irvine, Irvine, CA, USA.*

Sleep Disorders and Circadian Rhythm

429. The Circadian Protein Bmal1 Mediates Cell Type-Specific Effects on Protein Aggregation and Neuronal Survival in Mouse Models of Synucleinopathy and Tauopathy

*Patrick W. Sheehan, BS, Michael F. Kanan, BS, Collin J. Nadarajah, BS, Jessica N. Haines, MS, Tirth K. Patel, MD, PhD, **Albert A. Davis, MD, PhD**, Erik S. Musiek, MD, PhD. Washington University School of Medicine, St Louis, MO, USA.*

430. A Correlational Meta-Analysis Investigating Sleep Quality and Episodic Memory Performance at the Behavioral and Neural Level in Young and Older Adults

***Emily Hokett, MS**, Audrey Duarte, PhD. Georgia Institute of Technology, Atlanta, GA, USA.*

431. Effects of Solriamfetol on Driving Performance in Participants with Narcolepsy

***Frederick Vinckenbosch, MSc**[1], Gert Jan Lammers, PhD[2], Sebastiaan Overeem, MD, PhD[3], Dan Chen, MD, PhD[4], Grace Wang, MD, MS[4], Lawrence Carter, PhD[4], Kefei Zhou, PhD[4], Johannes Ramaekers, PhD[1], Annemiek Vermeeren, PhD[1]. [1]Maastricht University, Maastricht, Netherlands, [2]Sleep-Wake Centre SEIN, Zwolle, Netherlands, [3]Sleep Medicine Center Kempenhaeghe, Heeze, Netherlands, [4]Jazz Pharmaceuticals, Palo Alto, CA, USA.*

432. Alcohol Dependence as Enantiopathy to Cataplexy

***Gabriela Da Silva, MD**[1], Paolo-Emmanuel Perez, BA[2], Alan R. Hirsch, MD[1]. [1]Smell and Taste Treatment and Research Foundation, Chicago, IL, USA, [2]Cebu Doctors' University College of Medicine, Mandaue City, Philippines.*

433. Cataplexy-Free Days during Sodium Oxybate Treatment in Children and Adolescents with Narcolepsy with Cataplexy

***Emmanuel Mignot, MD, PhD**[1], Carol L. Rosen, MD[2], Diane Menno, PhD[3], Y. Grace Wang, MD[4], Judi Profant, PhD, CBSM[4], Yves Dauvilliers, MD, PhD[5,6]. [1]Stanford Center for Sleep Sciences and Medicine, Redwood City, CA, USA, [2]Division of Pediatric Pulmonology and Sleep Medicine, University Hospitals Cleveland Medical Center, Rainbow Babies &*

Children's Hospital, Cleveland, OH, USA, [3]Formerly Jazz Pharmaceuticals, Inc., Philadelphia, PA, USA, [4]Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [5]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France, [6]University of Montpellier, INSERM U1061, Montpellier, France.

434. Sodium Oxybate Treatment Effects on Sleep Architecture in Pediatric Patients with Narcolepsy with Cataplexy

***Emmanuel Mignot, MD**[1], Richard K. Bogan, MD[2], Jed Black, MD[3], Rupa Parvataneni, MS[3], Y. Grace Wang, MD[3], Yves Dauvilliers, MD, PhD[4]. [1]Stanford University Center for Narcolepsy, Redwood City, CA, USA, [2]University of South Carolina School of Medicine, Columbia, SC, USA, [3]Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [4]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France.*

435. Non-Invasive Calcium Imaging Reliably Classifies Sleep States

***Eric C. Landsness, MD PhD**, Wei Chen, N/A, Lindsey M. Brier, BS, Hua X. Rachel, N/A, Zach P. Rosenthal, BS, Joeseph C. Culver, PhD, Jin Moo Lee, MD PhD. Washington University St. Louis, St. Louis, MO, USA.*

436. Efficacy and Safety of JZP-258 in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study in Adults with Narcolepsy with Cataplexy

***Nancy Foldvary-Schaefer, DO, MS**[1], Richard K. Bogan, MD[2], Michael J. Thorpy, MD[3], Yves Dauvilliers, MD, PhD[4,5], Rafael Del Rio Villegas, MD, PhD[6], Markku Partinen, MD, PhD[7], Roman Skowronski, MD, PhD[8], Lihua Tang, PhD[9], Franck Skobieranda, MD[10], Karel Šonka, MD, PhD[11]. [1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, [2]University of South Carolina School of Medicine, Columbia, SC, USA, [3]Albert Einstein College of Medicine, Bronx, NY, USA, [4]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France, [5]University of Montpellier, INSERM U1061, Montpellier, France, [6]Neurophysiology and Sleep Disorders Unit, Hospital Vithas Nuestra Señora de America, Madrid, Spain, [7]Helsinki Sleep Clinic, Vitalmed Research Center, Helsinki, Finland, [8]Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [9]Formerly Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [10]Jazz Pharmaceuticals, Inc., Philadelphia, PA, USA, [11]First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic.*

437. JZP-258 Dose Titration and Transition from Sodium Oxybate in a Placebo-Controlled, Double-Blind, Randomized Withdrawal Study in Adult Participants with Narcolepsy with Cataplexy

***Nancy Foldvary-Schaefer, DO, MS**[1], Richard K. Bogan, MD[2], Michael J. Thorpy, MD[3], Lin Huang, PhD[4], Roman Skowronski, MD, PhD[4], Yves Dauvilliers, MD, PhD[5,6]. [1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, [2]University of South Carolina School of Medicine, Columbia, SC, USA, [3]Albert Einstein College of Medicine, Bronx, NY, USA, [4]Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [5]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France, [6]University of Montpellier, INSERM U1061, Montpellier, France.*

438. Cataplexy-Free Days in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of JZP-258 in Adults with Narcolepsy with Cataplexy

***Yves Dauvilliers, MD, PhD**[1,2], Nancy Foldvary-Schaefer, DO, MS[3], Richard K. Bogan, MD[4], Karel Šonka, MD, PhD[5], Judi Profant, PhD, CBSM[6], Lin Huang, PhD[6], Michael J. Thorpy, MD[7]. [1]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France, [2]University of Montpellier, INSERM U1061, Montpellier, France, [3]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, [4]University of South Carolina School of Medicine, Columbia, SC, USA, [5]First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic, [6]Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [7]Albert Einstein College of Medicine, Bronx, NY, USA.*

439. Identification of a Molecular Basis for the Juvenile Sleep State

***Leela Chakravarti Dilley, PhD**[1], Milan Szuperak, PhD[1], Naihua N. Gong, BS[1], Charlette E. Williams, BS[1], Ricardo Linares Saldana, BS[1], David S. Garbe, PhD[1], Mubarak Hussain Syed, PhD[2], Rajan Jain, MD, PhD[1], Matthew S. Kayser, MD, PhD[1]. [1]University of Pennsylvania, Philadelphia, PA, USA, [2]University of New Mexico, Albuquerque, NM, USA.*

440. Validation of Actigraphy for Sleep Measurement in Children with Cerebral Palsy

***Amy K. Licis, MD, MSCI**, Bing Xue, M.Sc., Jill Boyd, BS, Catherine Hoyt, PhD, Yo-EL S. Ju, MD, MSCI. Washington University School of Medicine, St. Louis, MO, USA.*

441. Long-Term Effects of Solriamfetol on Functioning and Work Productivity in Participants with Excessive Daytime Sleepiness Associated with Narcolepsy

***Atul Malhotra, MD**[1], Terri E. Weaver, PhD[2], Richard Schwab, MD[3], Colin Shapiro, PhD, MBBCh[4], Jan Hedner, MD[5], Mansoor Ahmed, MD[6], Patrick J. Strollo, MD[7], Geert Mayer, MD[8], Michelle Baladi, PhD[9], Morgan Bron, PharmD, MS[9], Patricia Chandler, MD[9], Lawrence Lee, PhD[9], Nancy Foldvary-Schaefer, DO, MS[10]. [1]University of California San Diego, La Jolla, CA, USA, [2]College of Nursing, University of Illinois at Chicago, Chicago, IL, USA, [3]University of Pennsylvania, Philadelphia, PA, USA, [4]University of Toronto, Toronto, ON, Canada, [5]Sahlgrenska University Hospital, Gothenburg,*

Sweden, [6]Cleveland Sleep Research Center, Cleveland, OH, USA, [7]University of Pittsburgh/Veterans Administration Pittsburgh Health System, Pittsburgh, PA, USA, [8]Hephata Klinik, Philipps University, Schwalmstadt, Germany, [9]Jazz Pharmaceuticals, Palo Alto, CA, USA, [10]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA.

442. Access to Sleep Care in Patients with Mild Traumatic Brain Injury

Tracy Chang, MD, Stefan Sillau, PhD, Brooke Valdez, BS, Lisa Brenner, PhD, ***Jean Tsai, MD PhD****. University of Colorado School of Medicine, Aurora, CO, USA.*

443. Changes in Cataplexy Frequency by Therapy at Study Entry in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of JZP-258 in Adults with Narcolepsy with Cataplexy

Michael J. Thorpy, MD*[1], Karel Šonka, MD, PhD[2], Richard K. Bogan, MD[3], Markku Partinen, MD, PhD[4], Rafael Del Rio Villegas, MD, PhD[5], Nancy Foldvary-Schaefer, DO, MS[6], Roman Skowronski, MD, PhD[7], Lihua Tang, PhD[8], Franck Skobieranda, MD[9], Yves Dauvilliers, MD, PhD[10,11]. [1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic, [3]University of South Carolina School of Medicine, Columbia, SC, USA, [4]Helsinki Sleep Clinic, Vitalmed Research Center, Helsinki, Finland, [5]Neurophysiology and Sleep Disorders Unit, Hospital Vithas Nuestra Señora de America, Madrid, Spain, [6]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, [7]Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [8]Formerly Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [9]Jazz Pharmaceuticals, Inc., Philadelphia, PA, USA, [10]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France, [11]University of Montpellier, INSERM U1061, Montpellier, France.*

444. Quality of Life in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of JZP-258 in Adults with Narcolepsy with Cataplexy

Nancy Foldvary-Schaefer, DO, MS*[1], Michael J. Thorpy, MD[2], Yves Dauvilliers, MD, PhD[3,4], Asim Roy, MD[5], Lihua Tang, PhD[6], Roman Skowronski, MD, PhD[7], Karel Šonka, MD, PhD[8], Richard K. Bogan, MD,[9]. [1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, Montpellier, France, [4]University of Montpellier, INSERM U1061, Montpellier, France, [5]Ohio Sleep Medicine Institute, Dublin, OH, USA, [6]Formerly Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [7]Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, [8]First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic, [9]University of South Carolina School of Medicine, Columbia, SC, USA.*

445. Prevalence, Incidence and Chronicity of Hypersomnolence Symptoms in the General Population

Ohayon M. Ohayon, MD, DSc, PhD*. Stanford University, Palo Alto, CA, USA.*

446. Longitudinal Survey of Idiopathic Hypersomnolence Disorders in the General Population

Ohayon M. Ohayon, MD, DSc, PhD*. Stanford University, Palo Alto, CA, USA.*

447. Clinically Relevant Effects of Solriamfetol on Excessive Daytime Sleepiness: A Post-Hoc Analysis of the Magnitude of Change in a Clinical Trial of Adults with Narcolepsy

Russell Rosenberg, PhD*[1], Michelle Baladi, PhD[2], Morgan Bron, PharmD, MS[3]. [1]NeuroTrials Research, Inc, Atlanta, GA, USA, [2]Jazz Pharmaceuticals, Palo Alto, CA, USA, [3]Former employee of Jazz Pharmaceuticals, Palo Alto, CA, USA.*

448. Kleine-Levin Syndrome is Associated with Trank1 Gene Variants in Conjunction with Birth Difficulties

Aditya Ambati, PhD*[1], Ryan Hillary, BS[1], Smaranda Leu-Semenescu, MD[2], Hanna M. Ollila, PhD[1], Ling Lin, MD PhD[1], Isabelle Arnulf, MD PhD[3], Emmanuel Mignot, MD PhD[1]. [1]Stanford Univeristy, Palo Alto, CA, USA, [2]Pitié-Salpêtrière Hospital, APHP, National Reference Center for Narcolepsy, Idiopathic Hypersomnia and Kleine–Levin Syndrome, Sorbonne University, Paris, France, [3]Sleep Disorders Unit (Department "R3S"), Pitié-Salpêtrière Hospital, APHP, National Reference Center for Narcolepsy, Idiopathic Hypersomnia and Kleine–Levin Syndrome, Sorbonne University, Palo Alto, CA, USA.*

449. Sleep Disordered Breathing in Intracerebral Hemorrhage Survivors in Japan: A Meta-Analysis & Systematic Review

Farhan Ishaq, MD MPH*. Neuroscience Institution, Geisinger Medical Center, Danville, PA, USA.*

450. Cholinergic Innervation of Genioglossus Motoneurons in the Context of Sleep Apnea

Krutika Joshi, PhD*, Jianguo Niu, PhD, Audrey Worley, BSc, Veronique G. VanderHorst, MD, PhD. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.*

451. African-Americans Exhibit Lower Sleep Efficiency and CSF Alzheimer Biomarker Levels Than Non-Hispanic Whites

Nithya Chennupati, BS*, Maggie Zangrilli, CCRC RPSGT, Suzanne Schindler, MD PhD, Anne M. Fagan, PhD, Yo-El Ju, MD MSCI. Washington University, Saint Louis, MO, USA.*

Friday Poster Presentations

Movement Disorders

452. *APOE* Genotype Regulates Pathology and Disease Progression in Synucleinopathy

Albert A. Davis, MD, PhD[1], *Casey E. Inman, BS*[1], *Zachary M. Wargel, BS*[1], *Umber Dube, BS*[1], *Brittany M. Freeberg, MS*[1], *Alexander Galluppi, BS*[1], *Jessica N. Haines, MS*[1], *Dhruva D. Dhavale, PhD*[1], *Rebecca Miller, PhD*[1], *Fahim A. Choudhury*[1], *Patrick M. Sullivan, PhD*[2], *Carlos Cruchaga, PhD*[1], *Joel S. Perlmutter, MD*[1], *Jason D. Ulrich, PhD*[1], *Bruno A. Benitez, MD*[1], *Paul T. Kotzbauer, MD, PhD*[1], *David M. Holtzman, MD*[1]. [1]*Washington University School of Medicine, St Louis, MO, USA,* [2]*Duke University Medical Center, Durham, NC, USA.*

453. Phantom Limb Pain Associated with Restless Limbs Syndrome: A Dopamine Responsive Disorder

David J. Dickoff, MD[1], *Nicholas J. Bellacicco, BA*[2]. [1]*Metropolitan Neurological Consultants. PC, Yonkers, NY, USA,* [2]*LECOM-Bradenton, Bradenton, FL, USA.*

454. A Multidisciplinary, Innovative Care Model for Dystonia - One Center's Unique Structure of Comprehensive and Individualized Treatment

Duarte Machado, MD, *Joy Antonelle deMarcaida, MD. Hartford Healthcare, Hartford, CT, USA.*

455. Increased Serum Neurofilament Light Chain Levels in Spinocerebellar Ataxia

Hye-Rim Shin, MSc[1], *Jangsup Moon, PhD*[2], *Woo-Jin Lee, MSc*[3], *Han Sang Lee, MSc*[3], *Eun Young Kim, MSc*[4], *Soon-Tae Lee, PhD*[3], *Keun-Hwa Jung, PhD*[3], *Kyung-Il Park, Doctor*[5], *Ki-Young Jung, PhD*[3], *Manho Kim, PhD*[3], *Sang Kun Lee, PhD*[3], *Kon Chu, PhD*[3]. [1]*Department of Neurology, Dankook University Hospital, Cheonan, Chungnam, Korea, Republic of,* [2]*Rare Disease Center, Seoul National University Hospital, Seoul, Korea, Republic of,* [3]*Department of Neurology, Seoul National University Hospital, Seoul, Korea, Republic of,* [4]*Department of Neurology, Chungnam National University Hospital, Daejeon, Korea, Republic of,* [5]*Department of Neurology, Seoul National University Healthcare System Gangnam Center, Seoul, Korea, Republic of.*

456. Spinal Segmental Myoclonus Associated with Episodes of Autonomic Dysreflexia in an Individual Living with Tetraplegia: A Case Report

Julio C. Furlan, MD, LLB, MBA, PhD, MSc, FRCPC[1], *Suvorit Bhowmick, MD*[2], *Robert E. Chen, MA, MSc, MB BCh, MB BChir*[3], *Alborz Oshidari, MD, FRCPC*[4], *Lesley Carr, MD, FRCPC*[5], *Anthony E. Lang, OC, MD, FRCPC, FAAN, FCAHS, FRSC*[3]. [1]*KITE - Toronto Rehabilitation Institute, University Health Network; and University of Toronto, Toronto, ON, Canada,* [2]*Toronto Western Hospital, University Health Network, Toronto, ON, Canada,* [3]*Toronto Western Hospital, University Health Network; and University of Toronto, Toronto, ON, Canada,* [4]*Toronto Rehabilitation Institute, University Health Network; and University of Toronto, Toronto, ON, Canada,* [5]*Sunnybrook Health Sciences Centre; and University of Toronto, Toronto, ON, Canada.*

457. Nilotinib Alters microRNAs That Regulate Specific Autophagy and Ubiquitination Genes in the CSF of Individuals with Parkinson's Disease

Yasar Torres-Yaghi, MD, *Fernando Pagan, MD, Charbel Moussa, MBBS PhD. Georgetown University Hospital, Washington, DC, USA.*

458. Variants in Saposin D Domain of Prosaposin Gene are Linked to Parkinson's Disease

Yutaka Oji, MD, PhD[1], *Taku Hatano, MD, PhD*[1], *Shin-Ichi Ueno, MD, PhD*[1], *Manabu Funayama, PhD*[1], *Kei-ichi Ishikawa, MD, PhD*[1], *Ayami Okuzumi, MD, PhD*[1], *Sachiko Noda, BSc*[1], *Shigeto Sato, MD, PhD*[1], *Wataru Satake, MD, PhD*[2], *Tatsushi Toda, MD, PhD*[2], *Yuanzhe Li, PhD*[1], *Tomoko Hino-Takai, PhD*[3], *Soichiro Kakuta, PhD*[1], *Taiji Tsunemi, MD, PhD*[1], *Hiroyo Yoshino, PhD*[1], *Kenya Nishioka, MD, PhD*[1], *Tatsuya Hattori, PD, PhD*[4], *Yasuaki Mizutani, PD, PhD*[5], *Tatsuro Mutoh, MD, PhD*[5], *Fusako Yokochi, PD, PhD*[6], *Yuta Ichinose, MD, PhD*[7], *Kishin Koh, MD, PhD*[7], *Kazumasa Shindo, MD, PhD*[7], *Yoshihisa Takiyama, MD, PhD*[7], *Tsuyoshi Hamaguchi, MD, PhD*[8], *Masahito Yamada, MD, PhD*[8], *Matthew J. Farrer, PhD*[9], *Yasuo Uchiyama, MD, PhD*[1], *Wado Akamatsu, MD, PhD*[1], *Yih-Ru Wu, MD*[10], *Junko Matsuda, MD, PhD*[3], *Nobutaka Hattori, MD, PhD*[1]. [1]*Juntendo University School of Medicine, Tokyo, Japan,* [2]*University of Tokyo, Tokyo, Japan,* [3]*Kawasaki Medical School, Okayama, Japan,* [4]*Hommachi Clinic, Aichi, Japan,* [5]*Fujita Health University, Aichi, Japan,* [6]*Tokyo Metropolitan Neurological Hospital, Tokyo, Japan,* [7]*University of Yamanashi, Yamanashi, Japan,* [8]*Kanazawa University, Ishikawa, Japan,* [9]*University of Florida, Florida, FL, USA,* [10]*Chang Gung Memorial Hospital, Taoyuan, Taiwan.*

459. Phantogeusia in Parkinson Disease Responsive to Sweet Cereals

Madhusudan Patel, MD[1], *Karla Licona, MPH*[2], *Alan R. Hirsch, MD*[1]. [1]*Smell & Taste Treatment & Research Foundation, Chicago, IL, USA,* [2]*All Saints University School of Medicine, Roseau, Dominica.*

460. Critical Glial Role for Parkinson's Disease Risk Genes in Controlling Alpha-Synuclein Toxicity

Abby Olsen, MD, PhD, *Mel Feany, MD, PhD. Brigham and Women's Hospital, Boston, MA, USA.*

461. A Novel Small Molecule Tyrosine Kinase Inhibitor (GUtinib) Preferentially Targets Discoidin Domain Receptors and Reduces Toxic Proteins in Neurodegeneration

***Charbel Moussa, MBBS PhD**, Yasar Torres-Yaghi, MD, Fernando Pagan, MD. Georgetown University Hospital, Washington, DC, USA.*

462. Efficacy and Safety of the T-Type Calcium Channel Modulator CX-8998 in T-CALM, a Randomized, Double-Blind, Placebo-Controlled, Phase 2a Trial in Participants with Essential Tremor

***William Ondo, MD**[1], Spyros Papapetropoulos, MD[2], Margaret S. Lee, PhD[3], Stacey Versavel, PhD[4], Andrew Krouse, MD[5], Evan Newbold, BS[3], Hyder A. Jinnah, MD[6], Rajesh Pahwa, MD[7], Kelly E. Lyons, PhD[7], Theresa Zesiewicz, MD[8], Peter Hedera, MD[9], Adrian Handforth, MD[10], Jenna Elder, PhD[11], Mark Versavel, MD[12], Rodger Elble, MD[13]. [1]Houston Methodist Neurological Institute, Weill Cornell Medical School, Houston, TX, USA, [2]Massachusetts General Hospital Department of Neurology, Boston, MA, USA, [3]Jazz Pharmaceuticals, Philadelphia, PA, USA, [4]Cerevel Therapeutics, LLC, Boston, MA, USA, [5]University of Virginia Licensing & Ventures Group, Charlottesville, VA, USA, [6]Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA, [7]Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA, [8]University of South Florida Ataxia Research Center, Tampa, FL, USA, [9]Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA, [10]VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA, [11]PharPoint Research, Inc., Wilmington, NC, USA, [12]vZenium, LLC, Arlington, MA, USA, [13]Department of Neurology, Southern Illinois University School of Medicine, Springfield, IL, USA.*

463. HIV Protease Inhibitors Activate the Integrated Stress Response and Correct Diverse Dystonia Phenotypes in Mouse Models

***Zachary F. Caffall, MS**[1], Bradley Wilkes, PhD[2], Ricardo Hernández-Martinez, PhD[1], Joseph Rittiner, PhD[1], Jennifer T. Fox, PhD[3], Min Shen, PhD[3], Mirand K. Shipman, BS[1], Kanny Wan, PhD[3], Steven A. Titus, PhD[3], Zhuyin Li, PhD[3], Matthew B. Boxer, PhD[3], Matthew D. Hall, PhD[3], David E. Vaillancourt, PhD[2], Nicole Calakos, MD,PhD[1]. [1]Duke University, Durham, NC, USA, [2]University of Florida, Gainesville, FL, USA, [3]National Center for Advancing Translational Sciences, Rockville, MD, USA.*

464. Objective Dystonia Identification Helps Elucidate Dystonia Pathophysiology

***Bhooma R. Aravamuthan, MD, DPhil**, Keisuke Ueda, MD, Hanyang Miao, B.S., Laura Gilbert, MD, MBA, Sarah E. Smith, B.S., Toni S. Pearson, MD, Jordan G. McCall, PhD, MPH. Washington University School of Medicine, St. Louis, MO, USA.*

465. Disparities in Access to Care and Research Participation in Advanced Parkinson's Disease: Differences between a Home Visit Study and Outpatient Clinic Population

***Jori E. Fleisher, MD MSCE**[1], Ellen C. Klostermann, PhD[1], Erica B. Myrick, MS[1], Serena P. Hess, MSN[1], Jeanette Lee, LCSW[1], Bichun Ouyang, PhD[1], Deborah A. Hall, MD PhD[1], Joshua Chodosh, MD MSHS[2,3]. [1]Rush University Medical Center, Chicago, IL, USA, [2]New York University Grossman School of Medicine, New York, NY, USA, [3]VA New York Harbor Healthcare System, New York, NY, USA.*

466. Optimizing Patient-Specific Computational Models of DBS Using Intraoperative Electrocorticography

*Bryan Howell, PhD[1], Faical Isbaine, PhD[2], Jon T. Willie, MD, PhD[2], Enrico Opri, PhD[2], Robert E. Gross, MD, PhD[2], Coralie De Hemptinne, PhD[3], Philip A. Starr, MD, PhD[3], Cameron C. McIntyre, PhD[1], **Svjetlana Miocinovic, MD, PhD**[2]. [1]Case Western Reserve University, Cleveland, OH, USA, [2]Emory University, Atlanta, GA, USA, [3]University of California San Francisco, San Francisco, CA, USA.*

467. The Molecular Integration in Neurological Diagnosis Parkinson's Disease Observational Study: MIND-PD

***Thomas F. Tropea, DO**, Noor Amari, BS, Noah Han, BS, EunRan Suh, PhD, Vivianna VanDeerlin, MD PhD, Alice Chen-Plotkin, MD PhD. University of Pennsylvania, Philadelphia, PA, USA.*

468. Acquired Movement Disorders Secondary to Tumefactive Virchow Robin Spaces

***Anthony Donigian, B.S.**, David N. Toupin, M.D., Zain Guduru, M.D. University of Kentucky College of Medicine, Lexington, KY, USA.*

469. Levetiracetam for Sleep Disturbances in Huntington's Disease

***Harsh Desai, MS**, Ajaz Sheikh, MD, Mehmood Rashid, MD. University of Toledo College of Medicine and Life Sciences, Toledo, OH, USA.*

470. Association between Fatigue and Motor Progression in Parkinson's Disease in Southern Chinese

***Hongxiang Yu, M.D.**, Meng-Ruo Guo, B.S., Gang Li, M.D.,Ph.D., Bei Zhang, M.D. Department of Neurology, East Hospital, Tongji University School of Medicine, Shanghai, China.*

471. Deficits in Postural Stability in Parkinson's Disease Patients with Freezing of Gait

***Kunal Shah, BS**, Lakshmi Pillai, MS, Aliyah Glover, BS, Tuhin Virmani, MD PhD. University of Arkansas of Medical Sciences, Little Rock, AR, USA.*

472. Abdominal Wall Dyskinesia

Leyla Y. Cavdar, BS, *Solomon O. Ajasin, BS, Scott Woolf, MD, Robert Fekete, MD. New York Medical College, Valhalla NY, NY, USA.*

473. The Paradox of The Pianist: A Case Report on the Violation of Fitt's Law in Piano Performance at Different Tempi in a Patient with Cerebellar Tremors

Pauline B. Roxas, Doctorate of Medicine (MD)[1], *Alan R. Hirsch, Doctorate of Medicine (MD)*[2]. [1]*Dr. Jose P Rizal School of Medicine, Xavier University - Ateneo De Cagayan, Cagayan De Oro City, Philippines,* [2]*The Smell and Taste Research Institute, Chicago, IL, USA.*

474. Slower Progression in Double Mutation *GBA-LRRK2*(G2019S) Associated Parkinson Disease

Roberto A. Ortega, MS[1], *Cuiling Wang, PhD*[2,3], *Deborah Raymond, MS*[1], *Fion Chu, BS*[1], *Roy N. Alcalay, MD, MS*[4], *Anat Mirelman, PhD*[5,6], *Yuliya Kuras, PhD*[7], *Clemens R. Scherzer, MD*[7], *Karen S. Marder, MD, MPH*[4], *Nir Giladi, MD*[5,6], *Susan B. Bressman, MD*[1], *Rachel Saunders-Pullman, MD, MPH*[1]. [1]*Department of Neurology, Mount Sinai Beth Israel, New York, NY, USA,* [2]*Department of Epidemiology and Family Health, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA,* [3]*Department of Neurology, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA,* [4]*Department of Neurology, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA,* [5]*Laboratory for Early Markers of Neurodegeneration (LEMON), Center for the Study of Movement, Cognition, and Mobility, Neurological Institute, Tel Aviv, Israel,* [6]*Tel Aviv Sourasky Medical Center, Tel Aviv, Israel,* [7]*Center for Advanced Parkinson Research, Harvard Medical School, Brigham & Women's Hospital, Boston, MA, USA.*

475. Long-Term Goal Achievement and Satisfaction after Deep Brain Stimulation in Parkinson's Disease

Seon Kyung Nam, BS[1], *Dallah Yoo, MD*[2], *Beomseok Jeon, MD, PhD*[2]. [1]*University of South Florida Morsani College of Medicine, Tampa, FL, USA,* [2]*Seoul National University Hospital, Seoul, Korea, Republic of.*

476. Comparing Rates of Motor Progression before and after DBS among Patients with Idiopathic and LRRK2-Associated Parkinson's Disease

Aaron C. Viser, BA[1], *Katherine Leaver, MD*[2], *Joan Miravite, DNP*[2], *Brian H. Kopell, MD*[2], *Robert Ortega, MS*[2], *Deborah Raymond, MS*[2], *Susan B. Bressman, MD*[2], *Rachel Saunders-Pullman, MD, MPH*[2], *Marta San Luciano, MD, MS*[1]. [1]*Department of Neurology, Weill Institute for Neurosciences - University of California, San Francisco, San Francisco, CA, USA,* [2]*Department of Neurology, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, New York, NY, USA.*

477. Effect of Opicapone and Entacapone on Early Morning-OFF Pattern in Parkinson's Disease Patients with Motor Fluctuations

Aleksandar Videnovic, MD, MSc[1], *Werner Poewe, MD*[2], *Andrew J. Lees, MD*[3], *Joaquim J. Ferreira, MD, PhD*[4], *Olga Klepitskaya, MD*[5], *Rui Loureiro, PhD*[6], *Diogo Magalhães, MD*[6,7], *José-Francisco Rocha, BsC*[6], *Patrício Soares-da-Silva, MD, PhD*[6,8]. [1]*Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA,* [2]*Medical University of Innsbruck, Innsbruck, Austria,* [3]*National Hospital for Neurology and Neurosurgery, London, United Kingdom,* [4]*Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal,* [5]*Neurocrine Biosciences, Inc., San Diego, CA, USA,* [6]*BIAL – Portela & Ca S.A., Coronado, Portugal,* [7]*University of Porto, Porto, Portugal,* [8]*University of Porto and MedInUP-Center for Drug Discovery and Innovative Medicines, Porto, Portugal.*

478. Exploring Populations for Intervention at an Urban VA Medical Center

Brandon R. Barton, MD, MS. *Jesse Brown VA Medical Center, Chicago, IL, USA.*

479. Istradefylline, an Adenosine A_{2A} Receptor Antagonist, as Adjunct to Levodopa in Parkinson's Disease (PD): A Pooled Safety Analysis of 4 Randomized Controlled Trials

Rajesh Pahwa, MD[1], *Keizo Toyama, MSc*[2], *Jeff Parno, MS*[3], *Deborah Braccia, PhD, MPA*[4], ***Brittany Cross, PhD***[4], *Akihisa Mori, PhD*[2]. [1]*University of Kansas Medical Center, Kansas City, KS, USA,* [2]*Kyowa Kirin Co., Ltd., Tokyo, Japan,* [3]*Kyowa Kirin Pharmaceutical Development, Inc., Princeton, NJ, USA,* [4]*Kyowa Kirin, Inc., Bedminster, NJ, USA.*

480. Relationship of Cerebrospinal Fluid Vitamin B12 Status Markers with Parkinson's Disease Progression

Chad Christine, MD[1], *Peggy Auinger, MS*[2], *Nasrin Saleh, MD*[3], *Miao Tian, MD PhD*[4], *Teodoro Bottiglieri, PhD*[5], *Erland Arning, PhD*[5], *Nam Tran, PhD*[3], *Per Ueland, MD, PhD*[6], *Ralph Green, MD, PhD*[3]. [1]*University of California San Francisco, San Francisco, CA, USA,* [2]*University of Rochester, Rochester, NY, USA,* [3]*University of California Davis, Sacramento, CA, USA,* [4]*University of California, Davis, Sacramento, CA, USA,* [5]*Baylor Scott & White Research Institute, Dallas, TX, USA,* [6]*Bevital, Bergen, Norway.*

481. Nilotinib Increases Brain Dopamine and Lowers CSF Tau and Oligomeric Alpha-Synuclein in Parkinson's Disease

Charbel Moussa, MBBS PhD, *Yasar Torres-Yaghi, MD, Fernando Pagan, MD. Georgetown University Hospital, Washington, DC, USA.*

482. A Pooled Analysis of Four Pivotal Randomized Controlled Trials of Istradefylline, an Adenosine A_{2A} Receptor Antagonist: Efficacy as Adjunct to Levodopa in Parkinson's Disease (PD)

Cheryl Waters, MD[1], *Keizo Toyama, MSc*[2], *Jeff Parno, MS*[3], *Deborah Braccia, PhD, MPA*[4], *Akihisa Mori, PhD*[2]. [1]*Division of Movement Disorders and Parkinson Disease, Columbia University, New York, NY, USA,* [2]*Kyowa Kirin Co., Ltd., Tokyo, Japan,* [3]*Kyowa Kirin Pharmaceutical Development, Inc., Princeton, NJ, USA,* [4]*Kyowa Kirin, Inc., Bedminster, NJ, USA.*

483. Safety and Pharmacokinetics of ATH434 (PBT434), a Novel Small Molecule Inhibitor of α-Synuclein Aggregation, in Adult and Older Adult Volunteers

David A. Stamler, MD[1], *Margaret Bradbury, PhD*[1], *Cynthia Wong, MPH*[1], *Elliot Offman, PhD*[2]. [1]*Alterity Therapeutics, Newark, CA, USA,* [2]*Certara Strategic Consulting, Montreal, QC, Canada.*

484. Nilotinib is Reasonably Safe and May Halt the Disease Progression in Moderately Severe Parkinson's Disease Patients

Fernando Pagan, MD*, Yasar Torres-Yaghi, MD, Charbel Moussa, MD. Georgetown University Hospital, Washington, DC, USA.*

485. Onset of Drug-Related Adverse Events in Parkinson's Disease Patients with Motor Fluctuations Treated with Opicapone in Clinical Practice: OPTIPARK Post-Hoc Analysis

Andrew J. Lees, MD[1], *Heinz Reichmann, MD, PhD*[2], *José-Francisco Rocha, BSc*[3], *Diogo Magalhães, MD*[3], ***Grace S. Liang, MD***[4], *Patrício Soares-da-Silva, MD, PhD*[3,5]. [1]*National Hospital for Neurology and Neurosurgery, London, United Kingdom,* [2]*University of Dresden, Dresden, Germany,* [3]*BIAL – Portela & Ca S.A., Coronado, Portugal,* [4]*Neurocrine Biosciences, Inc., San Diego, CA, USA,* [5]*University of Porto and MedInUP-Center for Drug Discovery and Innovative Medicines, Porto, Portugal.*

486. Parkinson Disease Symptoms and the Company They Keep as Reported Directly by 21,649 Patients

IRA Shoulson, MD[1], *Lakshmi Arbatti, MS*[2], *Abhishek Hosamath, MS*[2], *Monica Javidnia, PhD*[1], *David Oakes, PhD*[1], *Shirley Eberly, MS*[1], *Connie Marras, MD PhD*[3], *David Standaert, MD PhD*[4], *Caroline M. Tanner, MD PhD*[5], *Luba Smolensky, MS*[6], *Jamie Hamilton, PhD*[6], *Catherine Kopil, PhD*[6], *Carol A. Christopher, PhD*[2], *Andrew Nguyen, PhD*[7]. [1]*University of Rochester, Rochester, NY, USA,* [2]*Grey Matter Technologies, Sarasota, FL, USA,* [3]*University of Toronto, Toronto, ON, Canada,* [4]*University of Alabama Birmingham, Birmingham, AL, USA,* [5]*University of California San Francisco, San Francisco, CA, USA,* [6]*Michael J Fox Foundation for Parkinson's Research, New York, NY, USA,* [7]*University of San Francisco, San Francisco, CA, USA.*

487. The Utility of [^{123}I] Ioflupane Spect Imaging in African-American Patients: A Retrospective Chart Review Study

Juebin Huang, MD, PhD[1], *Catherine A. Kronfol, BS*[1], *Vani Vijayakumar, MD*[2]. [1]*University of Mississippi Medical Center, Jackson, MS, USA,* [2]*University of Mississippi Medical Center, Madison, MS, USA.*

488. Safety and Tolerability of Bone Marrow-Derived Allogeneic Mesenchymal Stem Cells in Parkinson's Disease Patients

Mya C. Schiess, MD[1], *Jessika Suescun, MD*[1], *Marie-Francoise Doursout, PhD*[1], *Christopher Adams, MD*[1], *Charles Green, PhD*[1], *Jerome G. Saltarrelli, PhD*[1], *Sean Savitz, MD*[1], *Timothy Ellmore, PhD*[2]. [1]*The University of Texas Health Science Center at Houston, Houston, TX, USA,* [2]*City University of New York, New York, NY, USA.*

489. Long-Term Efficacy of Opicapone in the Reduction of On-Time with Troublesome Dyskinesia in Parkinson's Disease Patients with Motor Fluctuations and Reporting Troublesome Dyskinesia

Fabrizio Stocchi, MD[1], *Joaquim J. Ferreira, MD, PhD*[2], ***Olga Klepitskaya, MD***[3], *Diogo Magalhães, MD*[4,5], *José-Francisco Rocha, BSc*[4], *Patrício Soares-da-Silva, MD, PhD*[4,5]. [1]*Department of Neurology, IRCCS San Raffaele Pisana, Rome, Italy,* [2]*Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal,* [3]*Neurocrine Biosciences, Inc., San Diego, CA, USA,* [4]*BIAL – Portela & Ca S.A., Coronado, Portugal,* [5]*University of Porto, Porto, Portugal.*

490. Efficacy of Opicapone at Different Levodopa Regimens up to a Threshold of 600mg/Day Levodopa in Parkinson's Disease Patients with Motor Fluctuations

Peter A. LeWitt, MD[1], *Fabrizio Stocchi, MD*[2], *Joaquim J. Ferreira, MD, PhD*[3], *Olga Klepitskaya, MD*[4], *Diogo Magalhães, MD*[5,6], *José-Francisco Rocha, BSc*[5], *Patrício Soares-da-Silva, MD, PhD*[5,6]. [1]*Henry Ford Hospital and Department of Neurology, Wayne State University School of Medicine, West Bloomfield, MI, USA,* [2]*Department of Neurology, IRCCS San Raffaele Pisana, Rome, Italy,* [3]*Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal,* [4]*Neurocrine Biosciences, Inc., San Diego, CA, USA,* [5]*BIAL – Portela & Ca S.A., Coronado, Portugal,* [6]*University of Porto, Porto, Portugal.*

491. Coincidental POLG Mutation Found in a Case of Drug-Induced Parkinsonism

Pretty Sara Idiculla, MBBS[1], *Syed Taimour Hussain, Medical Student*[2], *Talha Naser Jilani, MBBS*[3], *Junaid Habib Siddiqui, MD*[1]. [1]*University of Missouri, Columbia, MO, USA,*

[2]United Medical and Dental College, Karachi, Pakistan, [3]JFK Medical Center Neuriscience Institute, Edison, NJ, USA.

492. A Case of Novel CACNA1A Mutation Causing Type 2 Episodic Ataxia

***Pretty Sara Idiculla, MBBS**, Junaid Habib Siddiqui, MD. University of Missouri, Columbia, MO, USA.*

493. Characterization of the Pattern of Daily Motor Fluctuations in Parkinson's Disease Patients Based on Home Diaries

***Robert A. Hauser, MD, MBA**[1], Werner Poewe, MD[2], Joaquim J. Ferreira, MD, PhD[3], Andrew J. Lees, MD[4], Grace S. Liang, MD[5], Miguel Fonseca, PhD[6], Diogo Magalhães, MD[6,7], José-Francisco Rocha, BsC[6], Patrício Soares-da-Silva, MD, PhD[6,8]. [1]University of South Florida, Tampa, FL, USA, [2]Medical University of Innsbruck, Innsbruck, Austria, [3]Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal, [4]National Hospital for Neurology and Neurosurgery, London, United Kingdom, [5]Neurocrine Biosciences, Inc., San Diego, CA, USA, [6]BIAL – Portela & Ca S.A., Coronado, Portugal, [7]University of Porto, Porto, Portugal, [8]University of Porto and MedInUP-Center for Drug Discovery and Innovative Medicines, Porto, Portugal.*

494. Effects of Once-Daily Opicapone on Duration of Overnight OFF and Time to Morning ON in Patients with Parkinson's Disease and Motor Fluctuations

***Robert A. Hauser, MD, MBA**[1], Mark F. Lew, MD[2], Aleksandar Videnovic, MD, MSc[3], Werner Poewe, MD[4], Olivier Rascol, MD, PhD[5], Joaquim J. Ferreira, MD, PhD[6], Grace S. Liang, MD[7], Kurt Olson, MS[7], Khodayar Farahmand, PharmD[7], Chirag Shah, PharmD[7], José-Francisco Rocha, BsC[8], Patrício Soares-da-Silva, MD, PhD[8,9], Olga Klepitskaya, MD[7]. [1]University of South Florida, Tampa, FL, USA, [2]University of Southern California, Los Angeles, CA, USA, [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, [4]Medical University of Innsbruck, Innsbruck, Austria, [5]Toulouse University Hospital, Toulouse, France, [6]Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal, [7]Neurocrine Biosciences, Inc., San Diego, CA, USA, [8]BIAL – Portela & Ca S.A., Coronado, Portugal, [9]University of Porto and MedInUP-Center for Drug Discovery and Innovative Medicines, Porto, Portugal.*

495. Incidence and Survival of Psychosis in Patients with Parkinson's Disease (1991-2010)

***Rodolfo Savica, MD PhD**. Mayo Clinic, Rochester, MN, USA.*

496. Risk of Hospital Admission in Patients with Parkinson's Disease Associated Psychosis (1991-2010)

***Rodolfo Savica, MD PhD**. Mayo Clinic, Rochester, MN, USA.*

497. Association of Co-Morbid Hypertension, Diabetes Mellitus and Body Mass Index in Idiopathic Parkinson's Disease (PD), *LRRK2* Mutation PD and *GBA* Mutation PD

***Theresa Lin, B.A.**, Deborah Raymond, M.S., Sonya Elango, M.S., Katherine Leaver, M.D., Viktoriya Katsnelson, M.D., Nikita Urval, M.D., Leon Meytin, M.D., Sarah Simon, B.A., Fion Chu, B.A., Vicki Shanker, M.D., Matthew Swan, M.D., Naomi Lubarr, M.D., Mark Groves, M.D., Susan Bressman, M.D., Rachel Saunders-Pullman, M.D., MPH, Roberto Ortega, M.S. Mount Sinai Beth Israel, New York, NY, USA.*

498. Astrocyte-Converted Neurons Rescue Nigro-Striatal Circuit in Parkinson Disease Model

***William C. Mobley, M.D., Ph.D.**, Steven F. Dowdy, Ph.D., Don W. Cleveland, Ph.D., Hao Qian, M.D., Ph.D., Xiang-Dong Fu, Ph.D. University of California, San Diego, La Jolla, CA, USA.*

499. Cortical Synaptic and Mitochondrial Dysfunction in Mouse Models of Huntington's Disease

***Yingli Gu, PhD, MD**[1], Alexander Pope, master[1], Christopher Carmona, master[1], Xuqiao Chen, PhD[1], Claire Cecile Bacon-Brenes, undergraduate student[2], William C Mobley, PhD, MD[1], Chengbiao Wu, PhD[1]. [1]UCSD, San Diego, CA, USA, [2]Scripps College, San Diego, CA, USA.*

500. PBT434 Preserves Dopaminergic Neurons, Reduces α-Synuclein Oligomerization, and Improves Motor Function in a Transgenic Murine Multiple System Atrophy Model

***Antonio Heras-Garvin, PhD**[1], Violetta Refolo, PhD[1], Claudio Schmidt, BSc[1], Margaret Bradbury, PhD[2], David Stamler, MD[2], Nadia Stefanova, MD, PhD, DSc[1]. [1]Medical University of Innsbruck, Innsbruck, Austria, [2]Alterity Therapeutics, Newark, CA, USA.*

501. Genetic Risk Scores and Hallucinations in Parkinson's Disease Patients

***Cynthia Kusters, MD,PHD**[1], Kimberly Paul, MPH,PhD[1], Aline Duarte Folle, Ms,PhD[1], Adrienne Keener, MD[1], Jeff Bronstein, MPH,PhD[1], Valerija D. Dobricic, PhD[2], Ole-bjorn Tysnes, MD[3], Lars Bertram, MD,PhD[2], Guido Alves, MD,PhD[4], Janet Sinsheimer, PhD[1], Christina Lill, MD,PhD[2], Jodi Maple-Grodem, PhD[4], Beate Ritz, MD,PhD[1]. [1]University of California, Los Angeles, Los Angeles, CA, USA, [2]University of Luebeck, Luebeck, Germany, [3]University of Bergen, Bergen, Norway, [4]University of Stavenger, Stavenger, Norway.*

502. Mortality in Patients with Parkinson Disease Psychosis Receiving Pimavanserin and Quetiapine: A Retrospective Review

***Katherine Longardner, MD**, Brenton Wright, MD, Aljoharah Alakkas, MBBS, Fatta B. Nahab, MD. University of California San Diego, La Jolla, CA, USA.*

503. Early-Onset Parkinson Disease Screening in Patients from Nigeria

Lukasz M. Milanowski, MD[1], *Jennifer A. Lindemann, MSc*[2], *Alexandra I. Soto-Beasley, MSc*[2], *Ronald L. Walton, BSc*[2], *Rana H. Al-Shaikh, MD, MSc*[1], *Audrey J. Strongosky, C.C.R.C.*[1], *Zbigniew K. Wszolek, MD*[1], *Owen A. Ross, PhD*[3], *Olajumoke Oshinaike, MD*[4], *Shamsideen O. Ogun, MD*[4]. [1]*Department of Neurology, Mayo Clinic Florida, Jacksonville, FL, USA,* [2]*Department of Neuroscience, Mayo Clinic Florida, Jacksonville, FL, USA,* [3]*Department of Neuroscience, Neuroscience Track, Mayo Graduate School, Department of Clinical Genomics, Mayo Clinic Florida, Jacksonville, FL, USA,* [4]*Division of Neurology, Department of Medicine, Faculty of Clinical Sciences, College of Medicine, Lagos State University and Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria.*

504. The Association between *SNCA* Gene Top Parkinson's Disease Variants and Basal Ganglia Imaging Traits

Saud Alhusaini, MD PhD[1], *Mohamed Kandil, MD*[1], *Lynne Krohn, MSc*[2], *Mitja Mitrovic, PhD*[1], *Sara M. Schaefer, MD*[1], *Avram Holmes, PhD*[3], *Elan D. Louis, MD*[1], *Ziv Gan-OR, MD PhD*[2]. [1]*Yale School of Medicine, New Haven, CT, USA,* [2]*Montreal Neurological Institute, McGill University, Montreal, QC, Canada,* [3]*Yale University Psychology Department, New Haven, CT, USA.*

505. Understanding the Interaction between Gut Microbiome and the Brain through Machine Learning Based Modeling

Yosef G. Tirat-Gefen, PhD in Computer Engineering / Staff Fellow at FDA*. George Mason University / MaxWave Research LLC, Fairfax/VA and Rockville/MD, VA, USA.*

506. COPD/Asthma and Active Smoking History Associates Independently with Parkinson's Disease Outcome in an Essential Tremor Population

Alyssa M. Smith, MD*, Mudit Gupta, MS, Mihai C. Sandulescu, MD. Geisinger Health System, Danville, PA, USA.*

507. Impact of Race and Socioeconomic Status on the Utilization of Advanced Therapies in Parkinson's Disease

Jennifer Adrissi, M.D.[1], *Guanhong Miao, B.S.*[2], *Yichao Yu, PhD*[2], *Tanya Simuni, M.D.*[1]. [1]*Northwestern University Feinberg School of Medicine, Chicago, IL, USA,* [2]*University of Florida, Gainesville, FL, USA.*

508. Amantadine Therapy for Ataxia Management in Patients with Spinocerebellar Ataxia Type 7

Laura A. Pesantez Pacheco, MD*, Nivedita Thakur, MD. University of Texas Health Science Center at Houston, Houston, TX, USA.*

509. Sleep and Depression in Parkinson's Disease: Investigating the Relationship between Sleep and Depression Using a Combination of Subjective and Objective Sleep Assessment Methods

Philip Mulryan, MD*, Sean Affonso, MD, Aideen Sullivan, PhD. University College Cork, Cork, Ireland.*

510. Altered Capicua Expression Drives Regional Purkinje Neuron Vulnerability Through Ion Channel Gene Dysregulation in Spinocerebellar Ataxia Type 1

Ravi Chopra, MD, PhD[1], *David D. Bushart, PhD*[2], *John P. Cooper, BS*[3], *Dhananjay Yellajoshyula, PhD*[2], *Logan M. Morrison, BS*[2], *Haoran Huang, BS*[2], *Daniel R. Scoles, PhD*[4], *Stefan M. Pulst, MD*[4], *Harry T. Orr, PhD*[5], *Vikram G. Shakkottai, MD, PhD*[2]. [1]*Washington University in St. Louis, Saint Louis, MO, USA,* [2]*University of Michigan, Ann Arbor, MI, USA,* [3]*University of Texas at Austin, Austin, TX, USA,* [4]*University of Utah, Salt Lake City, UT, USA,* [5]*University of Minnesota, Minneapolis, MN, USA.*

511. Investigating a Novel Combination of Sensory Markers in Cervical Dystonia

David Ezana, BA (currently in progress)[1], *Aaditi G. Naik, BA*[1,2], *Grace Cannard, BA*[1], *Nia Mitchell, BS*[3], *Miranda Tomaras, BA*[1], *Jacqueline Meystedt, BA*[1], *David Charles, MD*[1], *Mallory L. Hacker, PhD, MSCI*[1,1]. [1]*Vanderbilt University, Nashville, TN, USA,* [2]*Pritzker School of Medicine, The University of Chicago, Chicago, IL, USA,* [3]*Georgia State University, Atlanta, GA, USA.*

K-579. *APOE* Genotype Regulates Pathology and Disease Progression in Synucleinopathy

Albert A. Davis, MD, PhD[1], *Casey E. Inman, BS*[1], *Zachary M. Wargel, BS*[1], *Umber Dube, BS*[1], *Brittany M. Freeberg, MS*[1], *Alexander Galluppi, BS*[1], *Jessica N. Haines, MS*[1], *Dhruva D. Dhavale, PhD*[1], *Rebecca Miller, PhD*[1], *Fahim A. Choudhury*[1], *Patrick M. Sullivan, PhD*[2], *Carlos Cruchaga, PhD*[1], *Joel S. Perlmutter, MD*[1], *Jason D. Ulrich, PhD*[1], *Bruno A. Benitez, MD*[1], *Paul T. Kotzbauer, MD, PhD*[1], *David M. Holtzman, MD*[1]. [1]*Washington University School of Medicine, St Louis, MO, USA,* [2]*Duke University Medical Center, Durham, NC, USA.*

K-580. Glucocerebrosidase Deficiency Mediates Propagation of Protein Aggregation in a *Drosophila* Model of Neurodegeneration via Modification of Extracellular Vesicles

Kathryn Jewett, PhD[1], *Ruth Thomas, PhD*[1], *Chi Phan, BA, MSci*[2], *Gillian Milstein, BS*[2], *Selina Yu, BS*[3,2], *Leo J. Pallanck, PhD*[2], ***Marie Y. Davis, MD PhD***[3,4]. [1]*University of Washington (Dept. Genome Sciences), Seattle, WA, USA,* [2]*University of Washington (Dept Genome Sciences), Seattle, WA, USA,* [3]*VA Puget Sound Healthcare System, Seattle, WA, USA,* [4]*University of Washington (Dept. Neurology), Seattle, WA, USA.*

Neuro-Oncology

512. In-Vivo Two-Photon Imaging Reveals Brain Capillary Plugging during Neurotoxicity in a Mouse Model of Chimeric Antigen Receptor (CAR) T Therapy

Juliane Gust, MD PhD[1,2], *Andy Y. Shih, PhD*[3,4]. [1]*Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA,* [2]*Department of Neurology, University of Washington, Seattle, WA, USA,* [3]*Center for Developmental Biology and Regenerative Medicine, Seattle Children's Research Institute, Seattle, WA, USA,* [4]*Department of Pediatrics, University of Washington, Seattle, WA, USA.*

513. Identification of Small Molecules, Proteins, and Nanoparticles That Bypass the Blood Brain Barrier Upon Intranasal Delivery

Kalen R. Dionne, MD, PhD*, Rui Tang, PhD, Krishna Sharmah Gautam, PhD, Kathleen Duncan, BS, Gail Sudlow, BS, Samuel Achilefu, PhD. Washington University, St. Louis, MO, USA.*

514. Bi-Specific Natural Killer Cell Engager (BiKE): A Novel Therapy for Glioblastoma

Kristen D. Raue, BS[1]*, Irina V. Balyasnikova, PhD*[2]. [1]*Rush University, Chicago, IL, USA,* [2]*Northwestern University, Chicago, IL, USA.*

515. Transposable Elements Offer Neoantigen Promise for Immunotherapy in Glioblastoma

Noah Basri, BA*, Hyo Sik Jang, PhD, Nakul M. Shah, MD, Ting Wang, PhD. Washington University School of Medicine, St. Louis, MO, USA.*

516. Streptococcus Intermedius Brain Abscess Mimicking Necrotic Tumor: Case Report

Seon K. Nam, BS[1]*, JooEun Kwon, BA*[1]*, John N. Greene, MD*[2]. [1]*USF Morsani College of Medicine, Tampa, FL, USA,* [2]*Moffitt Cancer Center, Tampa, FL, USA.*

517. Whole-Brain Resting-State Mapping to Measure the Effect of Gliomas on Brain Function

Erica Silvestri, PhD.[1,2]*, Manuela Moretto, MSc*[2]*, Marco Castellaro, PhD.*[3]*, Silvia Facchini, PhD.*[1]*, Elena Monai, MD*[1]*, Domenico D'Avella, MD*[1]*, Diego Cecchin, MD*[4,2]*, Alessandro Della Puppa, MD*[5]*, Alessandra Bertoldo, PhD.*[6,2]*, Maurizio Corbetta, MD*[1,2]. [1]*Department of Neuroscience, University of Padova, Padova, Italy,* [2]*Padova Neuroscience Center, Padova, Italy,* [3]*Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy,* [4]*Department of Medicine, Unit of Nuclear Medicine, University of Padova, Padova, Italy,* [5]*Department of Neurosurgery, University of Florence, Florence, Italy,* [6]*Department of Information Engineering, University of Padova, Padova, Italy.*

518. Exploring Patients' Subjective Experiences during Awake Craniotomies: Clinical Practices to Alleviate Patient Discomfort and Promote Resilience

Dana Dharmakaya Colgan, PhD[1]*, Ashley Eddy, MS*[2]*, Kaylie Green, MS*[2]*, Margarita Aulet-Leon, BA*[1]*, Seunggu J. Han, MD*[1]*, Ahmed Raslan, MD*[1]*, Barry Oken, MD*[1]*.* [1]*Oregon Health Sciences University -, Portland, OR, USA,* [2]*Pacific University, Portland, OR, USA.*

519. Acute-Onset Throbbing Headache, a Rare Manifestation of Sphenoid Wing Meningioma: A Case Report

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520. An Atypical Presentation of Lymphomatosis Cerebri

Ana Martinez-Tapia, M.D.[1]*, Christopher Folterman, M.D., M.S.*[2]*, Michel Ritenuti, D.O.*[1]. [1]*St. Luke's University Hospital, Bethlehem, PA, USA,* [2]*St. Barnabas Medical Center, Livingston, NJ, USA.*

521. Relapsed Diffuse Large B-cell Lymphoma (DLBCL) with Leptomeningeal Carcinomatosis Treated with Intrathecal Chemotherapy

Derek Neupert, MD*, Monica Noya Santana, MD, Justin Salerian, MD, Aimee Aysenne, MD, MPH. Tulane University School of Medicine, New Orleans, LA, USA.*

522. First Dose Pembrolizumab-Induced Toxicity in Young Patient Treated for Invasive Thymoma: An Overlap Syndrome of Myasthenia Gravis and Myositis

Dmitri Kovalev, MD[1]*, Alexandra Muranova, MD*[1]*, Chilvana Patel, MD*[2]. [1]*Univeristy of Texas Medical Branch, Galveston, TX, USA,* [2]*University of Texas Medical Branch, Galveston, TX, USA.*

523. Pre-Infusion Neurofilament Light Chain (NfL) Levels Predict the Development of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Omar H. Butt, MD, PhD*, Alice Y. Zhou, MD, PhD, Suzanne E. Schindler, MD, PhD, Anne M. Fagan, PhD, John F. Dipersio, MD, PhD, Armin Ghobadi, MD, Beau M. Ances, MD, PhD. Washington University, Saint Louis, MO, USA.*

524. Primary Lumbar Spinal Epidural B Lymphoblastic Lymphoma Initially Misdiagnosed as Chronic Back Pain

Shobha Mandal, MBBS,MD[1]*, Mary Grace Bethala, MD*[2]*, Philip Lowry, MD*[1]. [1]*Guthrie Robert Packer Hospital, Sayre, PA, USA,* [2]*GlobeHealer, Philadelphia, PA, USA.*

Dementia and Aging

525. Gamma Sensory Flicker for Patients with Prodromal Alzheimer's Disease: A Phase I Trial

Qiliang He, PhD[1], Kay Colon-Motas, MS[2], Alyssa Pybus, BS[1], Lydia Pendel, BS[2], Jonna Seppa, BS[2], Margaret Walker, PhD[2], Cecelia Manzanares, PhD[2], Deqiang Qui, PhD[2], Svjetlana Miocinovic, MD, PhD[2], Levi Wood, PhD[1], Allan Levey, MD, PhD[2], James Lah, MD, PhD[2], ***Annabelle C. Singer, PhD[1,2]****. [1]Georgia Institute of Technology, Atlanta, GA, USA, [2]Emory University, Atlanta, GA, USA.*

526. Deep Proteomic Analysis of Alzheimer Disease Brain Identifies New Protein Co-Expression Modules Associated with Disease That are Not Observed at the RNA Level

Erik C.B. Johnson, M.D., Ph.D.*, Eric B. Dammer, Ph.D., E. Kathleen Carter, Ph.D., Duc M. Duong, B.S., Lingyan Ping, Ph.D., Luming Yin, Ph.D., James J. Lah, M.D., Ph.D., Allan I. Levey, M.D., Ph.D., Nicholas T. Seyfried, Ph.D. Emory University, Atlanta, GA, USA.*

527. Life-Threatening Definitive Toxoplasmic Encephalitis as the First Manifestation in HIV Infections — Identification through Clinical and Paraclinical Features

Wali Qayoumi, MD, Treeva Jassim, MD, Katelyn Dolbec, MD, ***Mam Ibraheem, MD, MPH****. University of Kentucky-Department of Neurology, Lexington, KY, USA.*

528. Whole Genome CRISPR-i Screens Reveal How Loss of TDP-43 Function Causes Neuronal Death

Michael E. Ward, MD, PhD*, Sarah Hill, PhD. NINDS, NIH, Bethesda, MD, USA.*

529. Glycaemic Control, Diabetic Complications, and Risk of Dementia among 0.5 Million Diabetes Patients: A Cohort Study Using the UK Clinical Practice Research Datalink

Bang Zheng, MSc*, Bowen Su, MSc, Ioanna Tzoulaki, PhD, Sara Ahmadi Abhari, PhD, Lefkos Middleton, MD. Imperial College London, London, United Kingdom.*

530. Mutations in TREM2 Change the Expression Levels of AD-Related Genes

Tianyi Zhao, PhD[1]*, Liang Cheng, PhD[2]. [1]Harbin Institute of Technology, Harbin, China, [2]Harbin Medical School, Harbin, China.*

531. A Highly Sensitive Assay Does Not Detect Tau Seeding Activity in the Cerebrospinal Fluid of Alzheimer's Disease Patients

Brian Hitt, M.D., Ph.D. *UT Southwestern Medical Center, Dallas, TX, USA.*

532. History of Seizures in Alzheimer's Disease Patients is Associated with Elevations in mTOR Activity and Neuropathology

David A. Stewart, BS[1]*, Sarah Gourmaud, PhD[2], David J. Irwin, MD[3,2], Delia M. Talos, MD[2], Frances E. Jensen, MD[2]. [1]Duke University School of Medicine, Durham, NC, USA, [2]Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA, [3]Penn Frontotemporal Degeneration Center, University of Pennsylvania, Durham, NC, USA.*

533. The Association of Motoric Cognitive Risk with Neuroimaging and Incident Dementia: The ARIC Study

Gabriela T. Gomez, B.S.[1]*, Rebecca F. Gottesman, MD, PhD[1], B. Gwen Windham, MD, MHS[2], Priya Palta, PhD, MHS[3], Clifford R. Jack, Jr., MD[4], David S. Knopman, MD[4], Kevin J. Sullivan, PhD, MPH[2], Kelley P. Gabriel, PhD, MS[5], Alden Gross, PhD, MHS[6], Keenan Walker, PhD[1]. [1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]University of Mississippi Medical Center, Jackson, MS, USA, [3]Columbia University Medical Center, New York, NY, USA, [4]Mayo Clinic, Rochester, MN, USA, [5]The University of Alabama at Birmingham, Birmingham, AL, USA, [6]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.*

534. Modeling Ancestry Specific Differences in *APOE* Functionality Using Induced Pluripotent Stem Cell Models

Krisna S. Maddy, Bachelor of Arts*, Oded Oron, PhD, Chris Miquel, BA, Holly Cukier, PhD, Farid Rajabli, PhD, Catherine Garcia Serje, MS, Katrina Celis, MD, Natalia Hofmann, BS, Pedro Mena, MD, Kara Hamilton-Nelson, PhD, Margaret Pericak-Vance, PhD, Jeffery Vance, MD/PhD, Derek Dykxhoorn, PhD. University of Miami Miller School of Medicine, Miami, FL, USA.*

535. Nilotinib Effects on Safety, Tolerability, and Biomarkers in Alzheimer's Disease: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial

Charbel Moussa, MD, PhD*. Georgetown University Medical Center, Washington DC, DC, USA.*

536. PTPRD Roles Alzheimer's Disease Tau Pathophysiology

George Uhl, MD PhD*. University of New Mexico College of Medicine/NMVAHCS, Albuquerque, NM, USA.*

537. Associations between HIV, Antiretroviral Therapy and Risk of Early Onset Alzheimer's Disease

Guodong Liu, PhD*, Djibril Ba, MPH, Lan Kong, PhD, Chen Zhao, MD, MS, MA. Penn State University, Hershey, PA, USA.*

538. Longitudinal Anatomic, Functional and Molecular Characterization of Pick's Disease Phenotypes

Jennifer L. Whitwell, PhD[1], *Nirubol Tosakulwong, BS*[1], *Christopher C. Schwarz, PhD*[1], *Matthew L. Senjem, MS*[1], *Anthony J. Spychalla, BS*[1], *Joseph R. Duffy, PhD*[1], *Jonathan Graff-Radford, MD*[1], *Mary M. Machulda, PhD*[1], *Bradley F. Boeve, MD*[1], *David S. Knopman, MD*[1], *Ronald C. Petersen, MD*[1], *Val J. Lowe, MD*[1], *Clifford R. Jack, MD*[1], *Dennis W. Dickson, MD*[2], *Joseph E. Parisi, MD*[1], *Keith A. Josephs, MD*[1]. [1]*Mayo Clinic, Rochester, MN, USA,* [2]*Mayo Clinic, Jacksonville, FL, USA.*

539. A Randomized, Placebo-Controlled, Double-Blind Trial of the Plasma Fraction GRF6019 in Severe Alzheimer Disease

Jonas Hannestad, MD PhD[1], *Tiffanie Pederson, BS*[1], *Whitney Chao, BS*[1], *Katie Koborsi, MS*[1], *Vicki Klutzaritz, BS*[1], *Brian Beck, MD*[2], *Ashok K. Patel, MD*[3], *James Scott, MD PhD*[4], *Stephen G. Thein, PhD*[5], *Gary Kay, PhD*[6], *Steven P. Braithwaite, PhD*[1], *Karoly Nikolich, PhD*[1]. [1]*Alkahest, San Carlos, CA, USA,* [2]*CCT Research, Phoenix, AZ, USA,* [3]*BioBehavioral Health, Toms River, NJ, USA,* [4]*Riverside Clinical Research, Edgewater, FL, USA,* [5]*Pacific Research Network, San Diego, CA, USA,* [6]*Cognitive Research Corporation, St. Petersburg, FL, USA.*

540. Isolation of PU.1 Positive Nuclei from Post-Mortem Human Brain Allows Better Differentiation of Microglia Subtypes in Alzheimer's Disease

Kevin J. Green, B.S. *University of Washington, Seattle, WA, USA.*

541. Optimizing Aging in Flint Michigan Framework: Exploring Opportunities to Facilitate Successful Aging

Maria Cielito Robles, BS[1], *Alison O'Brien, MPH*[2], *Nishat Islam, BS, MPH*[2], *A. Camille McBride, BS, MPH*[2], *Casey L. Corches, MPH, MSOTR/L*[1], *Mellanie V. Springer, MD, MS*[1], *Lesli E. Skolarus, MD, MS*[1,2]. [1]*University of Michigan Medical School, Ann Arbor, MI, USA,* [2]*University of Michigan School of Public Health, Ann Arbor, MI, USA.*

542. DIAN-TU Alzheimer's Disease Prevention Trial of Solanezumab and Gantenerumab: Amyloid, Tau and Neurodegeneration Outcomes

Randall Bateman, MD[1], *Andrew Aschenbrenner, PhD*[1], *Tammie Benzinger, MD*[1], *David Clifford, MD*[1], *Carlos Cruchaga, PhD*[1], *Anne Fagan, PhD*[1], *Martin Farlow, MD*[2], *Alison Goate, DPhil*[3], *Brian Gordon, PhD*[1], *Jason Hassenstab, PhD*[1], *Clifford Jack, MD*[4], *Robert Koeppe, MD*[5], *Eric McDade, DO*[1], *Susan Mills, BS*[1], *John C. Morris, MD*[1], *Stephen Salloway, MD*[6,7], *Anna Santacruz, BS*[1], *Peter Snyder, PhD*[8], *Guoqiao Wang, PhD*[1], *Chengjie Xiong, PhD*[1], *Barbara J. Snider, MD*[1], *Catherine Mummery, MD*[9], *Ghulam Surti, MD*[7], *Hannequin Didier, MD*[10], *David Wallon, MD, PhD*[10], *Sarah Berman, MD, PhD*[11], *James Lah, MD, PhD*[12], *Ivonne Z. Jimenez-Velazquez, MD, FACP*[13], *Erik Roberson, MD, PhD*[14], *Christopher Van Dyck, MD*[15], *Lawrence S. Honig, MD, PhD*[16], *Raquel Sanchez Valle, MD, PhD*[17], *William S. Brooks, MBBS, MPH*[18], *Serge Gauthier, MD*[19], *Colin Masters, MBBS, MD*[20], *Douglas Galasko, MD*[21], *Jared Brosch, MD*[2], *Robin Hsiung, MD*[22], *Suman Jayadev, MD*[23], *Maite Formaglio, MD*[24], *Mario Masellis, MD*[25], *Roger Clarnette, MBBS, FRACP, PhD*[26], *Jeremie Pariente, MD*[27], *Bruno Dubois, MD*[28], *Florence Pasquier, MD, PhD*[29], *Scott Andersen, MD*[30], *Karen Holdridge, MD*[30], *Mark Mintun, MD*[31], *John Sims, MD*[30], *Roy Yaari, MD*[30], *Monika Baudler, MD*[32], *Paul Delmar, PhD*[32], *Rachelle Doody, MD, PhD*[32], *Paulo Fountouro, MD, PhD*[32], *Geoff Kerchner, MD, PhD*[32]. [1]*Washington University School of Medicine, St. Louis, MO, USA,* [2]*Indiana University, Indianapolis, IN, USA,* [3]*Mt. Sinai School of Medicine, New York, NY, USA,* [4]*Mayo Clinic, Rochester, MN, USA,* [5]*University of Michigan, Ann Arbor, MI, USA,* [6]*Warren Alpert Medical School of Brown Medical School, Providence, RI, USA,* [7]*Butler Hospital, Providence, RI, USA,* [8]*The University of Rhode Island, Providence, RI, USA,* [9]*University College London Hospital, London, United Kingdom,* [10]*Centre Hospitalier Universitaire Rouen, Rouen, France,* [11]*University of Pittsburgh, Pittsburgh, PA, USA,* [12]*Emory University, Atlanta, GA, USA,* [13]*University of Puerto Rico, Puerto Rico, PR, USA,* [14]*University of Alabama Medical Center, Birmingham, AL, USA,* [15]*Yale School of Medicine, New Haven, CT, USA,* [16]*Columbia University, New York, NY, USA,* [17]*Universitat de Barcelona, Barcelona, Spain,* [18]*Neuroscience Research Australia and University of New South Wales, Sydney, Australia,* [19]*The Douglas Research Centre, McGill University, Montreal, QC, Canada,* [20]*Florey Institute of Neuroscience and Mental Health, Victoria, Australia,* [21]*University of California San Diego, San Diego, CA, USA,* [22]*University of British Columbia, Vancouver, BC, Canada,* [23]*University of Washington, Seattle, WA, USA,* [24]*Hospitalier Neurologue chez Lyon, Pierre Wertheimer Hospital, Bron, France,* [25]*Sunnybrook Research Institute, Toronto, ON, Canada,* [26]*The University of Western Australia, Peth, Australia,* [27]*Hopital Pierre-Paul Riquet, Toulouse, France,* [28]*Neurological Institute of the Salpetriere University Hospital, Paris, France,* [29]*Universite Hospital of Lille, Lille, France,* [30]*Eli Lilly and Company, Indianapolis, IN, USA,* [31]*Avid Radiopharmaceuticals, Indianapolis, IN, USA,* [32]*Hoffman-LaRoche, Basel, Switzerland.*

543. Changes in Cognitive Performance in Patients with Decompensated Congestive Heart Failure

Rebecca F. Gottesman, MD PhD[1], *Nicole Williams, MS*[1], *Andrew Gaddis, MD*[1], *Yessenia Gomez, BS*[1], *Serban Negoita, BS*[2], *Indira Rayala, undergrad*[1], *Rosanne Rouf, MD*[3], *Tanya Simmons, RN*[1], *Natalia Sonsin-Diaz, BS*[1], *Nisha Chandra, MD*[1]. [1]*Johns Hopkins University, Baltimore, MD, USA,* [2]*University of Maryland, Baltimore, MD, USA,* [3]*University of Michigan, Ann Arbor, MI, USA.*

544. Biomarkers of Neurodegeneration Strongly Predict Neurocognitive Impairment in Virally Suppressed People with HIV

Ronald J. Ellis, MD, PhD[1], *Christos J. Petropoulos, PhD*[2], *John Winslow, PhD*[2], *Yolanda Lie, PhD*[2], *Ahmed Chenna, PhD*[2], *Melanie Crescini, BS*[1], *Scott L. Letendre, MD*[1].

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545. Morphologic Changes in Regional Brain Volumes during Healthy Aging Process through Automated Brain Segmentation

Soochul Park, MD., PhD.[1], *Myeongjee Lee, PhD.*[2], *Huije Che, MS*[1], *Hyeonjin Jeon, MS*[1], *Jinna Kim, MD., PhD.*[3]. [1]*Department of Neurology, Seoul, Korea, Republic of,* [2]*BCU, Department of Bimedical Systems Informatics, Seoul, Korea, Republic of,* [3]*Division of Head & Neck Neuroradiology, Department of Radiology, Seoul, Korea, Republic of.*

546. Human Gastrointestinal (GI) Tract Microbiome-Derived Neurotoxins - Contribution to Inflammatory Neurodegeneration in Alzheimer's Disease (AD) Brain

Walter Lukiw, BS, MS, PhD*. LSU Neuroscience Center, New Orleans, LA, USA.*

547. The Impact of Dual GRN and TMEM106b Knockout on Neuronal Survival and TDP-43 Pathology

Allison Snyder, MD*, Michael E. Ward, MD, PhD. National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA.*

548. Association between Serum Bicarbonate Levels and Cognitive Function among Older Community Dwelling Adults

Belen Nunez, MD[1], *Andrea Zammit, PhD*[2], *Mindy Katz, MPH*[2], *Carol Derby, PhD*[2], *Michal Melamed, MD*[3]. [1]*Montefiore Medical Center, Bronx, NY, USA,* [2]*Einstein Aging Study, Neurology Division, Albert Einstein College of Medicine, Bronx, NY, USA,* [3]*Nephrology Division, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, Bronx, NY, USA.*

549. Changes of Metabolic Connectivity in Visual Hallucinations Due to Dementia with Lewy Bodies

Giovanni Zorzi, MD[1], *Diego Cecchin, MD*[2], *Cinzia Busse, PhD*[3], *Maurizio Corbetta, MD*[4], *Annachiara Cagnin, MD*[3]. [1]*Padova Neuroscience Center, Padova, Italy,* [2]*Dept.Medicine University of Padova, Padova, Italy,* [3]*Clinica Neurologica Padova University Hospital, Padova, Italy,* [4]*Department of Neuroscience & Padova Neuroscience Center, Padova, Italy.*

550. Tau and Amyloid Relationships to Resting-State Functional Connectivity in Atypical Alzheimer's Disease

Irene Sintini, PhD*, Jonathan Graff-Radford, MD, David T. Jones, MD, Hugo Botha, MD, Peter R. Martin, MS, Mary M. Machulda, PhD, Christopher G. Schwarz, PhD, Matthew L. Senjem, MS, Jeffrey L. Gunter, PhD, Clifford R. Jack, Jr., MD, Val J. Lowe, MD, Keith A. Josephs, MD, Jennifer L. Whitwell, PhD. Mayo Clinic, Rochester, MN, USA.*

551. The Aphasic Presentation of Diffuse Lewy Body Disease

Marina Buciuc, MD, MS[1], *Jennifer L. Whitwell, PhD*[1], *Joseph R. Duffy, PhD*[1], *Mary M. Machulda, PhD*[1], *Malgorzata B. Franczak, MD*[2], *Neill R. Graff-Radford, MD*[3], *Dennis W. Dickson, MD*[3], *Keith A. Josephs, MD*[1]. [1]*Mayo Clinic, Rochester, MN, USA,* [2]*Medical College of Wisconsin, Milwaukee, WI, USA,* [3]*Mayo Clinic, Jacksonville, FL, USA.*

552. Accelerated Rate of Hippocampal Atrophy 17-Years Prior to Death in Alzheimer's Disease is Linked to TAR DNA Binding Protein 43

Marina Buciuc, MD, MS[1], *Peter R. Martin, MS*[1], *Stephen D. Weigand, MS*[1], *Nirubol Tosakulwong, BS*[1], *Melissa E. Murray, PhD*[2], *Leonard Petrucelli, PhD*[2], *Matthew L. Senjem, MS*[1], *Anthony J. Spychalla, BS*[1], *David S. Knopman, MD*[1], *Bradley F. Boeve, MD*[1], *Ronald C. Petersen, MD, PhD*[1], *Joseph E. Parisi, MD*[1], *Dennis W. Dickson, MD*[2], *Clifford R. Jack, Jr., MD*[1], *Jennifer L. Whitwell, PhD*[1], *Keith A. Josephs, MD, MST, MSc*[1]. [1]*Mayo Clinic, Rochester, MN, USA,* [2]*Mayo Clinic, Jacksonville, FL, USA.*

553. Tauopathy-Induced Gliovascular Dysfunction Identified by Cell-Specific Viral TRAP-seq

Yutaro Komuro, PhD*, Mitchell Rudd, BA, Jason D. Hinman, MD, PhD. UCLA, Los Angeles, CA, USA.*

554. Varied Clinical Presentations of a Rapidly Progressive Disease, Creutzfeldt Jakob - A Diagnostic Challenge

Adriana Mendez, M.D.*, Divisha Raheja, M.D., Aaron Lasker, M.D. St Luke's University Health Network, Easton, PA, USA.*

555. Early Occult Network Dysfunction in Cognitively-Normal *APOE*ε4 Carriers is Associated with Elevated CSF SNAP-25 Levels

Omar H. Butt, MD, PhD*, Suzanne E. Schindler, MD, PhD, Anne M. Fagan, PhD, Tammie L. Benzinger, MD, PhD, Carlos Cruchaga, PhD, John C. Morris, MD, Beau M. Ances, MD, PhD. Washington University, Saint Louis, MO, USA.*

556. Kv1.3 Channel Expressing Brain Myeloid Cells are a Unique Pro-Inflammatory Subset of Microglia Which Can Be Modulated by Kv1.3 Blockers in Alzheimer's Pathology

Supriya Ramesha, MD[1,2], *Tianwen Gao, MBBS*[1], *Cynthia Giver, MD*[1], *Sruti Rayaprolu, PhD*[1], *Ngozi Nwabueze, MD*[1], *Amanda Engstorm, PhD*[1], *Hailian Xiao, BS*[1], *Andrea Pennati, PhD*[3], *David Katz, PhD*[1], *Edmund K. Waller, MD*[1], *Allan I. Levey, MD*[1], *Srikant Rangaraju, MD*[1]. [1]*Emory University SOM, Atlanta, GA, USA,* [2]*West Virginia University,*

Morgantown, WV, USA, [3]University of Wisconsin-Madison, Madison, WI, USA.

557. Resolving the Aggregate Trends of APOE on Transgenic Alzheimers Mouse Cognition

***Caroline Tanzy, B.S.**, Jamie Hernandez Kluesner, B.S., Yassin Watson, B.S., Shreya Ramesh, B.S., Zoey Patel, B.S., Kaci Hernandez Kluesner, B.S., Brenae Nelson, B.S., Cassie S. Mitchell, Ph.D. Georgia Insitute of Technology, Atlanta, GA, USA.*

558. Early-Onset Frontotemporal Dementia in Patient with Retrotransposed Transcript of *Matrin-3* Variant 5: A Case Report

***Madelyn Castro, BS**[1], Nisha Venkateswaran, BA[1], Samuel T. Peters, BA[1], Kasey Ah Pook, BS[1], David R. Deyle, MD[2], Matthew Bower, MS[1], Michael D. Koob, PhD[1], Bradley F. Boeve, MD[2], Keith Vossel, MD, MSc[1]. [1]University of Minnesota, Minneapolis, MN, USA, [2]Mayo Clinic Rochester, Rochester, MN, USA.*

559. Association Rule Mining to Determine Pharmaceutical and Supplement Usage Associated with Alzheimers Disease

***Velda Wang, B.S.**, Jayant Prakash, M.S., Cassie S. Mitchell, Ph.D. Georgia Institute of Technology, Atlanta, GA, USA.*

K-576. Activity Dependent Regulation of CaMKII and Local RNA Translation Machinery in the Postsynaptic Density

*Yuyoung Joo, PhD, **David R. Benavides, MD, PhD**. University of Maryland School of Medicine, Baltimore, MD, USA.*

K-596. Synergistic Behavioral and Neuroinflammatory Effects of Amyloid Neuropathology and Sepsis Survival in a Murine Model of Alzheimer's Disease

*Angela C. Bustamante, PhD, Marc Padilla, BS, Michael Newstead, BS, **Benjamin H. Singer, MD, PhD**. University of Michigan, Ann Arbor, MI, USA.*

Education

560. Necessity of Systems Medicine, Neuroscience Outreach to Combat Covid-19

***Abhishek Dutta, PhD**. University of Connecticut, Storrs, CT, USA.*

561. Simulation for Neurologic Emergencies and Acute Scenarios (SNES) Course: A 4-Year Evolutionary Experience of Utilizing Simulation for Incoming PGY-2 Neurology Residents to Prepare Them for Independent Calls

***Christa Nobleza, MD**, Anna Lerant, MD, Robin Rockhold, PhD, Joyce Shelby, MBA, Patrick Parker, NRP, Shashank Shekhar, MD, Hartmut Uschmann, MD, Jeffrey Orledge, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

562. Neurological Aspects of Corona Virus Infectious Disease 2019 [COVID-19]

***Nitin Butala, MD MS**[1,2]. [1]LECOM, Bradenton, FL, USA, [2]Baptist Medical Center, Jacksonville, FL, USA.*

563. Gender's Influence on Career Success of Physician-Scientists in Neurology

***Jenna Brownrout, BA**, Gina Norato, MPH, Wyatt Bensken, BA, Catherine Squirewell, BA, Taylor Gordon, BA, John Heiss, MD, Avindra Nath, MD, Omar I. Khan, MD. National Institutes of Neurological Disorders and Stroke, Bethesda, MD, USA.*

564. CSF Cryptococcus Antigen Test, Trends and Epidemiology

***Sushma Edara, M.B.B.S**, Pradeep Bathina, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

565. Epidemiology and Outcomes for HIV Patients with Cryptococcal Meningitis

***Sushma Edara, M.B.B.S**, Pradeep Bathina, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

566. Case Report: Rhomboencephalosynapsis - A Unique Congenital Posterior Fossa Malformation

***Nina Navalkar, MD**[1], Edward Conner, MD[2]. [1]MD Program, Mercer University School of Medicine, Macon, GA, USA, [2]Neonatal Intensive Care Unit, Beverly Knight Olson Children's Hospital Navicent Health, Macon, GA, USA.*

567. Utility of Mobile Applications in Clinical Neurology

***Tamer G. Ghanayem, BA**[1], Yousaf Ajam, MD[2], Varun Shah, MD[2], Elena Shanina, MD[2]. [1]University of Texas Medical Branch, School of Medicine, Galveston, TX, USA, [2]University of Texas Medical Branch, Department of Neurology, Galveston, TX, USA.*

568. Hogwarts House Grouping for a Combined Wellness and Assessment Initiative for Resident Trainees in Neurology (Hogwarts-Neurology)

***Christa O'Hana Nobleza, MD**, Alexander Auchus, MD, Shashank Shekhar, MD, Shreyas Gangadhara, MD, Juebin Huang, MD, Mary Alissa Willis, MD, Hartmut Uschmann, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

569. Dysphagia from Long-Term Olanzapine Use- A Rare Adverse Effect

***Pretty Sara Idiculla, MBBS**, Lisa Morris, Medical Student, Junaid Habib Siddiqui, MD. University of Missouri, Columbia, MO, USA.*

570. Research Outcomes in Parkinson Disease Emerging Therapies: Impact of a Medical Education Program on Neurologists' Knowledge

***Thomas Finnegan, PhD**[1], Lisette Arnaud-Hevi, PhD[2], John Maeglin, BS[2], Michael S. Okun, MD[3]. [1]Medscape Education, Newtown Square, PA, USA, [2]Medscape Education, New York, NY, USA, [3]University of Florida Health, Gainesville, FL, USA.*

571. Online Medical Education Improves Knowledge among Neurologists Regarding the Relationship between Age and Immune System Function in Multiple Sclerosis

***Thomas Finnegan, PhD**[1], Catherine Murray, MS[2], John Maeglin, BS[2]. [1]Medscape Education, Newtown Square, PA, USA, [2]Medscape Education, New York, NY, USA.*

572. Brainwave about Brainwaves: A New Educational Initiative for Medical Students

***Vinita J. Acharya, MD**[1], Andrew J. Matrick, MD[2], Jayant N. Acharya, MD, DM[1]. [1]Penn State Hershey Medical Center, Hershey, PA, USA, [2]McGaw Medical Center of Northwestern University, Chicago, IL, USA.*

573. Improving the Comfortability of Neurology Residents in Providing Care for Spanish-Speaking Monolingual Patients during Neurologic Emergencies

***Jennifer Adrissi, M.D.**, Fan Caprio, M.D. Northwestern University Feinberg School of Medicine, Chicago, IL, USA.*

574. Enhancing High Yield Resident Education in a High Volume Comprehensive Stroke Center Vascular Neurology Service

***Tamra Ranasinghe, MD**[1], Melissa Moore, MD[2], Dawn Meyer, PhD[1], Umer Najib, MD[2], Ann Murray, MD[2], Gauri Pawar, MD[2]. [1]University of California San Diego, San Diego, CA, USA, [2]West Virginia University, Morgantown, WV, USA.*

575. Development of a Database Containing Detail Bedside Neurological Examination and Final Diagnosis

***Syou Ohtsuru, M.D.**[1], Syuichi Nagamatsu, M.D.[1], Hajime Arahata, M.D.[2], Naokazu Sasagasako, M.D. & PhD[3], Hirokazu Furuya, M.D. & PhD[1]. [1]Department of Neurology, Kochi Medical School, Kochi University, Nankoku, Kochi, Japan, [2]Department of Neurology, Neuro-Musclar Center, NHO Omuta Hospital, Omuta, Fukuoka, Japan, [3]Department of Neurology, Neuro-Mescular Center, NHO Omuta Hospital, Omuta, Fukuoka, Japan.*

ANA 2020 Abstracts

Autoimmune Neurology

392. A Rare Case of Recurrent Unilateral Facial Nerve Paralysis in a Patient with Neurosyphilis

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Background: Neurosyphilis can be categorized as early and late forms. Early forms of neurosyphilis typically affect the cerebral spinal fluid (CSF), meninges and the cranial nerves. Cranial nerves commonly involved are the optic, facial and auditory nerves. Recurrent paralysis of facial nerve is uncommon and has not been reported so far in association with neurosyphilis.

Case Presentation: A 66-year-old gentleman presented to the emergency department for sudden onset right facial weakness. His past medical history included neurosyphilis, dementia, prior recurrent right sided facial lower motor weakness in 1990's with no residual weakness. On examination, he had no change in his baseline impaired attention, concentration, and memory. He had new onset right lower motor neuron facial paralysis (House-Brackmann grade IV) with impaired taste sensation on the right half of tongue, with unremarkable remaining neurologic exam. He was diagnosed with neurosyphilis in June 2018 after positive CSF VDRL (Venereal Disease Research Lab) test, then completed antibiotic treatment with 2 weeks of IV Penicillin G followed by 3 injections of intra-muscular Benzathine penicillin. On current admission, his HIV test was negative. RPR (Rapid Plasma Reagin) quantitative test that was 1:256 in 2018, declined to 1:32 during current admission in 2020. Magnetic resonance imaging (MRI) Brain with contrast demonstrated linear facial nerve enhancement consistent with facial neuritis. He was started on high dose oral steroids, anti-viral (acyclovir) therapy for one week and later discharged home in stable condition.

Discussion: Neurosyphilis is fortunately a rare condition nowadays. Facial paralysis can be associated with it, but recurrent unilateral peripheral facial weakness has rarely been reported before in association with it.

Conclusions: Recurrent peripheral facial weakness may be a sign of an underlying neurosyphilis, a rare clinical syndrome nowadays. Our case highlights the importance of being vigilant about this rare clinical possibility.

393. A Rare Case of Miller Fisher Syndrome in Patient with History of Guillain-Barre Syndrome

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Introduction: Miller Fisher syndrome (MFS) is a variant of Guillain-Barre Syndrome (GBS) characterized by the triad of ataxia, ophthalmoplegia and areflexia. Antibodies against GQ1b (a ganglioside component of nerve) are present in 85-90% of patients with MFS.

Case Presentation: We present a case of 71 years old male with prior history of GBS, Diabetes mellitus type 2, who presented with chief complaint of ascending paresthesia progressing to gait imbalance, ptosis, ophthalmoplegia and dysphagia with antecedent upper respiratory tract infection. Neurological exam revealed complete ptosis, ophthalmoplegia and diminished gag reflex. He also had distal limb motor weakness and sensory impairment, with areflexia in all extremities. He was treated with 5-day course of Intravenous Immunoglobulin (IVIG). Cerebrospinal fluid analysis revealed albumin cytologic dissociation with positive Anti-GQ1b IgG antibodies while all the other antibodies for GBS were negative. His hospital course was complicated by Hemophilus Influenza pneumonia development and drop in pulmonary function test, that resolved with elective mechanical ventilation and intravenous antibiotics. Subsequently he underwent tracheostomy and percutaneous gastrostomy tube placement with slow improvement in the motor weakness and was discharged to Skilled Nursing Facility for rehabilitation. Of note, patient was diagnosed in 2009 with the classic Guillain Barré syndrome with ascending paraparesis, treated then with IVIG with a subsequent prolonged clinical course but with complete recovery.

Discussion: Several cases of MFS have been reported in the literature where patients have had many recurrences over subsequent years. Some of these cases had these recurrences as overlap syndrome with Bickerstaff encephalitis. Our case is unique because of the occurrence of MFS in a patient with prior remote history of the classic GBS. To our best knowledge, such a combination has not been reported before in the medical literature.

Conclusion: Miller Fisher Syndrome can occur in a patient with prior history of the classic Guillain-Barre Syndrome. This highlights the need for vigilance about such a rare occurrence.

394. A Retrospective, Cross-Sectional Study Evaluating Plasma Neurofilament Light Levels in Autoimmune Encephalitis

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Objective: To evaluate plasma neurofilament light (NfL) levels in autoimmune encephalitis (AE).

Background: Despite an incidence rate of 0.8/100,000 person-years in AE, individual antibody syndromes are rare. Each particular antibody syndrome has a different clinical phenotype, making one unifying clinical outcome measure difficult to assess as a group. However, the final common pathway is neuronal damage, suggesting that NfL may be a unifying biomarker of central nervous system injury that is easily obtainable through blood and may demonstrate a quantitative treatment response. NfL is a promising biomarker for neuronal injury that may predicting disease activity in other inflammatory diseases such as relapsing-remitting multiple sclerosis, but this has not been well studied in AE.

Design/methods: Patients were retrospectively identified who were enrolled in the biorepository at the Rocky Mountain MS Center at the University of Colorado. Patients had a well-defined autoimmune neurological disease and followed between 2014 and 2019. NfL was tested using the Single Molecule Array (SIMOA) technology (Quanterix). Levels >10 pg/ml were considered positive values based on normative control data.

Results: Twenty plasma and 8 CSF samples stored in the biorepository were evaluated. Elevated plasma levels of NfL were seen in patients with the various types of AE: GFAP), glutamic acid decarboxylase (GAD)-65, leucine-rich glioma-inactivated (LGI1), glycine receptor, and N-methyl-D-aspartate (NMDA) receptor antibodies. Higher NfL levels in the blood were found in untreated, acute presentations and subjects with active symptoms. Six of seven patients with levels >10pg/ml presented acutely. Patients within 6 months of presentation had plasma NfL that were higher (17.6 +/-22.4pg/ml) than those who were farther out from presentation (5.8+/-7.3pg/ml)(p=0.025) There is a positive correlation between plasma and CSF (r=0.74) with mean levels 39pg/ml higher in CSF.

Conclusions: Our findings support the use of plasma NfL as a potential non-invasive biomarker in patients with antibody-mediated AE.

395. Autoimmune Dysautonomia and Ataxia Due to Ganglionic Acetylcholine Receptor Autoantibodies

***Duarte Machado, MD**, Alison Carlson, APRN. Hartford Healthcare, Hartford, CT, USA.*

Objective: To report a rare case of a young woman presenting with dysautonomia and cerebellar ataxia due to ganglionic acetylcholine receptor antibodies causing autoimmune autonomic gangionopathy (AAG).

Background: AAG is a rare subacute disorder associated with antibodies against ganglionic acetylcholine receptors. Ganglionic acetylcholine receptor antibodies have been reported to also be associated with other neurological disorders unrelated to the autonomic nervous system, such as ataxia.

Design/Methods: Our patient is a 26 year old female who in March 2018 began having lightheadedness, stiffness in her neck and shoulder girdle, and difficulty lifting her arms. She also felt like just touch on her skin would cause muscle spasms, and muscle spasms would occur triggered by movement. She had frequent muscle spasms of the arms >legs, left>right, which caused her to fall a couple of times. She actually needed a walker at one point because of the leg stiffness. She had slurring of speech and limb ataxia. She was having to strain to urinate and also had constipation. She had abnormal sweating, and tended to sweat a lot at night. Cold especially triggered some spasms. Her exam was notable for gait imbalance, slurring of speech, and excessive saliva.

Results: Laboratory evaluation revealed an elevated α3-AChR Ab at 62 pmol/L (normal <53 pmol/L) with no other autoantibodies or infectious etiology detected. Thorough screening revealed no evidence of associated malignancy. Paraneoplastic panel otherwise only showed fluorescence on monkey cerebellum substrate, and IgG index was positive in CSF. She was subsequently started on intravenous immunoglobulin treatment.

Conclusions: AAG is a clinically heterogeneous disease with variable presentation, particularly in those with lower antibody titers. This case suggests including α3-AChR Ab in the evaluation of dysautonomia and cerebellar dysfunction in a young adult, and highlights the importance of further understanding α3-AChR within the brain.

396. Partial Stiff Person Syndrome as a Stroke Mimic

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Objective: To report a rare case of a patient presenting with unilateral symptoms whose work-up revealed partial stiff person syndrome (SPS).

Background: SPS is an immune-mediated neurological disorder characterized by rigidity of muscles, superimposed upon disabling spasms and heightened sensitivity to external stimuli. SPS is subdivided into several categories, including the classical type and its variants such as partial SPS.

Design/Methods: Our patient is a 62 year old female with no prior medical problem who presented to the hospital with right arm and leg weakness as well as a body locked sensation where she felt muscle stiffening and could not move. She also described random, large amplitude involuntary movements either in her right arm or right leg. No symptoms in her left side. She was admitted for suspected stroke in November 2018 and had extensive workup including MRI brain with contrast which did not show any area of enhancement nor acute DWI. No cause for her symptoms was found, and after discharge continued to have worsened right sided ataxia and hyperreflexia and increased muscle tone. Further work-up ensued, and it was not until April 2019 that she was found to have an elevated GAD (>250 IU/mL) and HbA1C 6.3 with positive islet cell antibody. Lumbar puncture results showed positive GAD65 Ab Assay (3.09 nmol/L) and the presence of oligoclonal bands.

Results: The patient was diagnosed with partial SPS, and was trialed on baclofen and then diazepam but did not tolerate these. She was subsequently started on intravenous immunoglobulin treatment, almost one year after the onset of her symptoms.

Conclusions: Partial SPS a subtype noted in only 10 to 15 % of patients, and classification gives important diagnostic and prognostic information. Recognition of classic SPS vs variants is important because appropriate therapy like IVIg improves symptoms in most patients and should be initiated without delay.

397. Neuronal Uptake, Antibody Binding, and Injury by Anti-Ma2 Antibodies in Organotypic Rat Brain Cultures: A Possible Direct Role for Paraneoplastic Autoantibody in Disease Pathogenesis

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Anti-Ma2 antibodies are paraneoplastic autoantibodies associated with syndromes of limbic, diencephalic, and brainstem

encephalitis in patients with testicular or other neoplasms. The role of anti-Ma2 antibodies in neuronal injury has not been defined, nor is it known whether these antibodies interact with their intracellular antigenic targets in living neurons. We have previously demonstrated that both anti-Yo and anti-Hu antibodies are taken up by neurons in rat organotypic brain cultures and that intracellular binding of these antibodies is followed by cell death. Here we examined whether neuronal uptake of anti-Ma2 antibodies also occurs in this culture system and whether uptake and cytotoxicity of anti-Ma2 antibodies *in vitr*o involved brain regions known to be affected in clinical disease. Organotypic cultures of rat hippocampus, brainstem and cerebellum were incubated with sera or cerebrospinal fluid (CSF) from 5 anti-Ma2 positive patients for intervals of up to 144 hours. Neuronal viability was determined using SYTOX dead cell staining. Cultures were then fixed, permeabilized, stained with Cy-5 conjugated anti-human IgG, and studied using confocal microscopy. Anti-Ma2 antibodies were taken up by neurons in brainstem and hippocampal cultures and accumulated in cytoplasm, nuclei, and granular structures in neuronal somata and processes. In affected neurons, a fraction of the granular structures containing anti-Ma2 antibodies also stained with antibodies to Staufen, an RNA binding protein which is known to be recruited into stress granules. Antibody uptake was associated with scattered neuronal death over the period of time studied. Uptake of anti-Ma2 by Purkinje or other cerebellar neurons was only rarely observed. Our study demonstrates neuronal uptake of anti-Ma2 antibody in hippocampal and brainstem cultures and shows that antibody uptake is followed by scattered neuronal death. The distribution of antibody uptake and neuronal injury differed from that seen with anti-Yo and anti-Hu antibodies and corresponded to the syndromes of clinical illness seen in human patients. Anti-Ma2 antibody may play a direct role in neuronal injury.

398. Magnetic Resonance Imaging Findings in *Cryptococcus Neoformans* Meningoencephalitis and Its Association with Clinical Outcomes

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Background: *Cryptococcus Neoformans* meningoencephalitis is a frequent CNS complication in immunocompromised patients. Combination of antifungal treatment agents including amphotericin is regarded as the standard treatment regimen, although still a significant portion of patients result in death. It is recently reported that leukocyte-bound or free-from cryptoccoci exit the venule of the brain and are accumulated in the peri-venular space, and be washed out to cause cryptococcal meningitis or invade in the brain parenchyma to develop an encephalitis. Therfore, MRI based imaging markers reflecting this cryptococcus specific phathomechanism might help elucidate the clinical course and predict the outcomes in the cryptococcal meningoencephalitis.

Methods: 55 patients diagnosed as cryptococcal meningitis and performed serial MRI evaluations were included in this study. Underlying immunological status, initial CSF profiles, acute treatment regimens, and treatment response (based on the CSF antigen/culture findings and clinical status) at 2, 7 weeks, and 6 months were evaluated. Baseline and follow-up MRI parameters included the presence of T2 signal intensity (SI) increment along the ependymal lining, expansion of T2 SI changes to adjacent periventricular white matter, presence of cryptococcoma, and hydrocephalus. Presence and grade of the enlarged periventricular space (ePVS) was also measured in the baseline MRI. Clinical outcomes were evaluated using mRS scores.

Results: At 6 months, 5(9.1%) patient died and 17 (30.9%) had poor neurological outcomes (mRS scores >2). T2 SI changes to adjacent periventricular white matter and cryptococcoma at baseline MRI was associated with 6-month mortality and poor outcomes. Patients with neurological deterioration were associated with interval development of periventricular white matter SI change, cryptococcoma, and hydrocephalus in follow-up MRI evaluations. Higher ePVS scores at baseline were associated with the neurological deterioration, progression of MRI findings, and poor outcomes.

Conclusion: The stagnation of CSF and subsequent invasion of cryptoccocus into brain parenchyma is associated with neurological deterioration and poor outcomes in the cryptococcal meningoencephalitis. MRI parameters might reflect the pathologic processes and be useful to predict outcomes.

399. Debilitating Human Herpesvirus 6 Myelitis (HHV-6) in an Immunocompetent Patient — Case Presentation and Literature Review

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Objective: Increase awareness of the rare presentation of HHV-6 myelitis and review literature for consensus guideline for the diagnosis and treatment.

Background: Neurologic complications associated with HHV-6, albeit rare, have been reported among both healthy and immunocompromised patients. HHV-6 can cause encephalitis in adults and is potentially fatal in immunosuppressed individuals. HHV-6 Myelitis, rare among adults, has generally been associated with immunosuppression. Given the rarity of this disease in immunocompetent individuals, there are no consensus statement on diagnostic and treatment approaches.

Design/Methods: We report debilitating HHV-6 myelitis in an immunocompetent patient who had significant neurologic recovery after rapid immunotherapies and valganciclovir.

Results: A middle-aged man presented with subacute progressive painless weakness in legs and bladder dysfunction with bowel dysmotility. No reported mental changes or seizures. No history of recent travel or known sick contacts. The patient had no history of immunologic, or rheumatologic disorders, and no immunosuppression. Neurologic examination revealed paraplegia and T2 myelopathy. MRI showed T2 hyperintense signal and slight cord expansion

from T7 to the conus with partial enhancement. CSF exam revealed 19 WBCs lymphocytic pleocytosis; CSF protein was 91 mg/dL. Extensive laboratory evaluation was unremarkable. The patient was provisionally diagnosed with idiopathic transverse myelitis, and was given treatment regimen of rapid immunotherapies. But HHV-6 DNA type B came back positive by quantitative PCR for 31,600 copy/ml in blood and for 39,700 copy/ml in CSF, and treated with valganciclovir. At two months follow-up visit, the patient has started ambulating by using a walker and no longer required urinary catheterizations.

Conclusions: HHV-6 myelitis should be considered in the differential diagnosis for adults presenting with subacute otherwise unexplained myelopathy symptoms, even immunocompetent patients. Increasing awareness of this rare presentation might facilitate timely diagnosis and treatment, and case reporting can clarify medical and epidemiological aspect of HHV-6 myelitis.

400. Probable Autoimmune Encephalitis without Detected Autoantibody: Clinical Characteristics and Treatment Response

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Background: Along with the rapidly expanding spectrum of autoimmune encephalitis (AE), AE with no detected autoantibody (AE-NoDAB) has become a major category of AE. We analyzed the clinical features, prognosis, and the efficacy of combination immunotherapy consisting of steroid, intravenous immunoglobulin (IVIG), rituximab, and tocilizumab (SIRT), in patients with AE-NoDAB.

Methods: In our institutional cohort of AE, 136 consecutive patients diagnosed with AE-NoDAB between 2014 and 2018 were included in this study. AE-NoDAB was subcategorized into autoimmune limbic encephalitis (ALE, 56 patients), acute disseminated encephalomyelitis (ADEM, 14 patients), and antibody-negative probable AE (probable-AE, 66 patients). Patients' two-year clinical severity was assessed at every week for the first 12 weeks, at every month for the next 9 months, and at every three months for the next 12 months, using the modified Rankin scale (mRS) and the Clinical Assessment Scales in Autoimmune Encephalitis (CASE). Immunotherapy regimens used up to each time point were categorized as SI, SIR, or SIRT. Patients were compared with 80 patients with antibody-positive AE.

Results: At last follow-up, 76 (55.9%) patients had favorable mRS outcomes (scores 0-2). No major difference was found between the baseline severity of antibody-positive AE and AE-NoDAB, but the outcome was worse in AE-NoDAB. The clinical features and the outcomes were comparable among the subcategories of AE-NoDAB. In linear mixed model analyses, poor outcome was associated with higher age and baseline CASE scores, and gray matter lesion involvement in the baseline MRI. The more combination of immunotherapy from SI to SIR and SIRT proved better outcomes. Subgroups with baseline cerebrospinal fluid leukocytosis or poor-prognostic features on the MRI were responsive not to SI but to SIR or SIRT. Early administration of SIR or SIRT, especially within one month, enhanced their clinical effect. Adverse events were frequent, but the combination immunotherapy was well-tolerated in most cases.

Conclusion: AE-NoDAB has distinct clinical features from antibody-positive AE. Early diagnosis and use of combined immunotherapy is warranted to improve the outcomes of AE-NoDAB. Some baseline parameters might help prognostication, establishing treatment strategies, and differential diagnosis.

401. Beyond the IgG4 Antibody Subclass in Musk Myasthenia Gravis: Novel Evidence for the Pathogenicity of IgG1,2 and 3

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Background: Muscle Specific Kinase myasthenia gravis (MuSK-MG) is an autoimmune disease that impairs neuromuscular transmission leading to generalised muscle weakness. MuSK, together with the downstream activation of DOK7, regulates a phosphorylation cascade leading to the clustering of acetylcholine receptors (AChRs) at the neuromuscular junction (NMJ) which also requires rearrangement of actin filaments by GTPases of the Rho family, and the anchoring of AChRs to the cytoskeleton by rapsyn. In MuSK-MG, monovalent MuSK-IgG4 autoantibodies inhibit MuSK phosphorylation dispersing AChR clusters. Divalent MuSK IgG1, 2 and 3 antibody subclasses co-exist at lower levels and also inhibit agrin-induced AChR clustering *in vitro*. As the mechanism of action of IgG1-3 is still unknown, our aim was to study further their effects *in vitro* on phosphorylation cascade, AChR clustering, and cytoskeleton modifications.

Methods: C2C12 myotubes were incubated with IgG1-3 or IgG4 antibodies purified from MuSK-MG patients. Phosphorylation levels of MuSK, DOK7, and βAChR, and the active form of Rho were analysed by western blotting. AChR clusters, rapsyn, and actin filaments were labelled by immunohistochemistry. Number and size of clusters, and their co-localisation with rapsyn were counted and analysed. Membrane expression of AChR was detected by radiolabelling with ^{125}I-bungarotoxin.

Results: AChR clustering was inhibited by all MuSK-IgG subclasses. However, IgG4 inhibited the phosphorylation cascade, whereas IgG1-3 increased MuSK, DOK7 and βAChR phosphorylation over time. In the presence of IgG1-3, phosphorylation of MuSK and DOK7 was consistently higher compared to agrin. Both IgG1-3 and IgG4 activated Rho GTPase similarly to agrin with no qualitative changes in rearrangement and structure of actin filaments. Notably, IgG1-3 partially increased AChR microclusters (<3 μm), disrupting cluster-rapsyn co-localisation, and reduced membrane expression of AChRs.

Conclusions: MuSK IgG1-3 and IgG4 both impair AChR clustering, but have an opposite effect on the phosphorylation cascade. We suggest that, due to their divalent binding to MuSK, IgG1-3 may induce an over-stimulation of the

phosphorylation pathway, determining initial formation of AChR microclusters but failing to sustain the full maturation of clusters. This is supported by the disruption of AChR-rapysn interaction and the decrease in AChR membrane expression.

402. Factors Associated with Exercise Participation in People with Multiple Sclerosis

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Background: Exercise can alleviate multiple sclerosis (MS) symptoms and improve quality of life. Walking and stretching are of particular value because they are low cost, can be performed by individuals with a wide range of abilities, and are recommended in recent exercise guidelines. Identifying factors associated with exercise participation is a priority for research in MS.

Objective: To describe associations between MS disability, demographics, insurance and income with exercising, and specifically walking and stretching, by pwMS in Oregon and Southwest Washington.

Methods: A cross-sectional survey querying demographics, MS treatment therapies, and exercise was distributed to pwMS (9/2018-4/2019). Exercise modalities queried included swimming, walking, water aerobics, stretching, yoga, tai chi and a write-in response. Logistic regression was used to examine associations between variables of interest and exercise participation (currently exercising, stretching, walking). Variables of interest were disease severity, current disease modifying medication, gender, race, ethnicity, education, insurance type, and income. Variables with $p<0.25$ in univariate models were added to a multivariate model, from which variables were eliminated using a stepwise procedure. The final models included those variables that remained significant, as well as age and MS subtype.

Results: 8,149 surveys were distributed. Some recipients received multiple survey opportunities. Completed surveys (≥75% items answered) were analyzed (n=1,010). Most respondents (n=832, 82%) reported exercising, with 58% of the total (n=586) stretching, and 58% (n=589) walking. In the final models, participants unable to walk had significantly lower odds of exercising than those with no/minimal disease severity (OR=0.36, 95%CI: 0.16, 0.80, p=0.01). Men also had lower odds of stretching compared to women (OR=0.67, 95%CI: 0.49, 0.92, p=0.01) and participants with moderate disease severity had higher odds of stretching compared to participants with no/minimal disease severity; (OR=1.55, 95%CI: 1.01, 2.38, p=0.046). Participants requiring some walking support or a walker had significantly lower odds of walking than those with no/minimal disease severity (OR=0.42, 95%CI: 0.26, 0.68, p<0.001; OR=0.25, 95%CI: 0.14, 0.45, p<0.001, respectively).

Conclusions: Although over 80% of this this cohort of pwMS reported exercising, those with greater disability were significantly less likely to exercise at all or to stretch than those with milder disability and men were less likely to stretch than women. These data support that exercise interventions targeted at pwMS with greater disability are needed.

403. Blepharospasm: Expanding the MOG Spectrum or Incidental Finding

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Objective: Describe and discuss a patient with blepharospasm and persistently positive myelin oligodendrocyte (MOG) antibodies.

Background: MOG antibodies are associated with optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, and other demyelinating syndromes in adults and children. The clinical spectrum of phenotypes associated with these antibodies is increasing since the availability of commercial testing. Movement disorders have been described in patients with aquaporin-4 anitbody positive neuromyelitis optica. These are most frequently observed in patients with spinal cord lesions. We describe a case of MOG antibodies in a patient with blepharospasm and no structural lesion.

Design/Methods: Retrospective chart review and literature search.

Results: A 68-year-old woman presented to neurology clinic in 2011 for involuntary eyelid closure. Her electrodiagnostic studies suggested possible chronic bilateral axonal facial neuropathy. Her brain magnetic resonance imaging showed normal parenchyma and normal volume for age. A diagnosis of blepharospasm was made. Botulinum toxin injections and a blepharoplasty procedure were performed without improvement. In 2013, she noted tightness of the lower face around the buccinator muscle with spontaneous nasal flaring. Her jaw tightness continued to worsen until 2018 when she had difficulty with mouth closure. Botulinum injections every four months improved her eyelid symptoms but did not improve her oromandibular dystonia. Clonazepam and Artane also proved unhelpful. MOG antibodies were tested when she presented for a second opinion. In 2019, her MOG FACS labs returned positive with an initial titer of 1:40 then a titer of 1:100 on repeat testing. She had no history or exam findings to suggest a prior optic neuritis or myelitis.

Conclusions: This case raises questions about the potential role of MOG antibodies in an uncommon movement disorder. Other considerations include false positive results due to cross reactivity with other auto-antibodies or seropositivity prior to the onset of a typical clinical phenotype associated with MOG.

404. Natural Language Processing Analyses of Written Text across Stages of Illness in Anti-NMDA Receptor Encephalitis

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Background: Anti-NMDA receptor encephalitis (anti-NMDARE) is a form of autoimmune encephalitis characterized by psychosis and seizures. Prior studies using natural

language processing (NLP) have shown that other disorders of psychosis, such as schizophrenia and its risk states, are characterized by decreased complexity of both semantics and syntax. In this small proof-of-principle study, we aimed to identify the linguistic features that characterized anti-NMDARE and determine whether these features could predict stage of illness.

Methods: Participants were asked to submit writing samples from set intervals before and after acute hospitalization (-12 months, -3 months, -1 month, +1 month, +12 months, and +24 months), provide demographic information, and complete a self-reported current symptoms assessment. Writing samples were de-identified. Data analysis was completed using an Information-Theoretic NLP model, which 1) categorized which time points best aligned as pre-illness, acute illness, and recovery and 2) identified the language-based features that were most predictive of this time point characterization.

Results: Writing samples from seven individuals with anti-NMDARE were analyzed. The selected NLP models identified -12 months as pre-illness; -3 months, -1 month, +1 month, and +12 months as acute illness; and +24 months as recovery. These models discriminated between pre-illness and acute illness with 80% accuracy (sensitivity 0.89, specificity 0.57, positive predictive value 0.84, and negative predictive value 0.67) and between pre-illness and recovery with 58% accuracy (sensitivity 0.40, specificity 0.71, positive predictive value 0.50, and negative predictive value 0.63). The features that contributed most significantly to each model comprised a total of 10 distinct complexity of syntax measures. There were no semantic measures found to contribute most significantly to either model.

Conclusions: In this proof-of-concept study, patients with anti-NMDARE appear to have characteristic changes in language from pre-illness to acute illness. While less prominent, there also appear to be changes from pre-illness to recovery, indicating either that recovery extends beyond 24 months or that long-term changes in language occur following this disease. The significant features driving these changes involve complexity of syntax and not semantics, suggesting implication of specific brain regions and necessitating future studies to interrogate the involvement of networks affected in anti-NMDARE. Next steps will examine how persistent changes in language associate with ongoing symptomology as well as explore the role of early language assessment in aiding diagnosis.

405. Guillain-Barre Syndrome after Platinum-Based Chemotherapy

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Introduction: Acute inflammatory demyelinating polyneuropathy (AIDP), one of the most common forms of Guillain-Barre Syndrome (GBS), usually occurs over several days and results in sensory loss and weakness. Preceding respiratory tract infection or gastrointestinal tract infection is reported by 70% of patients. Platinum based chemotherapy is widely used cytotoxic drug in cancer treatment recently shown to result in immune activation. This case focuses on the development of AIDP after treatment with a platinum-based chemotherapy agent.

Methods: Case report and literature review

Results: A 67-year-old male with rectal adenocarcinoma T4BN2M0 treated with FOLFOX (folinic acid, fluorouracil, oxaliplatin) presented with progressive weakness and dysphagia shortly after second cycle of treatment. On admission, two weeks after symptom onset the patient was bedbound with strength 0/5 in his lower and 3/5 in upper extremities. He had lower limb areflexia, diminished reflexes in his upper limbs, and distal predominant sensory loss. Clinical diagnosis of GBS was suspected and he underwent lumbar puncture, showing normal CSF protein, glucose and cell count. Nerve conduction study was consistent with AIDP, revealing low motor conduction velocities, prolonged distal latencies and temporal dispersion in upper extremities and unexcitable motor nerves in lower extremities. Sensory responses were absent in most nerves. Barium swallowing test showed significant oropharyngeal dysphagia. Serological markers of recent infection and paraneoplastic panel were negative. Patient was treated with IVIG and his platinum-based chemotherapy discontinued. He gradually improved strength and completely recovered. Two months later he was able to walk without assistance and tolerate normal diet. His chemotherapy regiment was changed to 5FU/Leucovorin.The PubMed search yielded 8 articles describing 11 patients with GBS after platinum-based chemotherapy. All except 2 cases received total cumulative platinum dose below established threshold for neurotoxicity, like our case. None had recent infection or vaccinations. Most patients had demyelinating form of GBS and severe disability (Modified Ranking scale at nadir 4-5), all but 1 patient developed dysphagia or respiratory symptoms. All reported patients were treated with 1-2 courses of IVIG with good recovery.

Conclusion: Platinum-based chemotherapy is known to cause neurotoxicity, but rarely associated with GBS. Prompt recognition and treatment of this condition in combination with platinum discontinuation is of utmost importance. Evidence of platinum induced elevation of tumor necrosis factor-alpha and interleukin-6 and enhanced anticancer immune responses support hypothesis of platinum activated immune reaction towards myelin antigens. The exact mechanisms remain to be confirmed.

406. Hashimoto Encephalopathy

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Hashimoto encephalopathy is a rare condition, with a prevalence of 2.1/100,000, more common in females. Some researchers believe that there's an association between Hashimoto encephalopathy and Hashimoto thyroiditis, the autoimmune process causing the inflammation and damage to vessels within the brain, presenting with stroke-like features. Some believe that it's just a coincidence since there's no evidence that anti-thyroid antibodies damage the brain causing

confusion, psychosis or coma. Even a specific level of antibodies doesn't correlate with the severity, however, more research is needed to grasp the precise reason behind the Hashimoto encephalopathy. [1,2] Considering that hypothyroidism is common and Hashimoto encephalopathy is rare (underdiagnosed due to nonspecific symptoms), every clinical case should be reported for more information accumulation and a better understanding of the clinical picture, genetic background, pathogenesis, diagnostic criteria, and treatment. The most common presenting symptom is a seizure (focal with secondary generalization), with a mechanism not fully understood. Genetics might be a contributing factor, besides, some researchers suggested that TSH effects and hypo-perfusion, also edema -induced cerebral dysfunction due to autoimmune-mediated vasculitis, may play a task within the mechanism of seizures. Recent ongoing researches about the efficacy of ocrelizumab and bortezomib are hopeful just in case the pathogenesis seems autoimmune. Recent studies have shown that T cell inhibitors: cyclosporine, tacrolimus, and sirolimus are successfully controlling the seizures. 3,4,5. Recent researches report that alpha-enolase and 36-kDa protein within the cerebral cortex may also play a role in HE. Another antibody under investigation is aldehyde reductase I, the antibody against parietal cells or intrinsic factor. They may become extra tools for diagnosing this condition.[6,7] There are no globally accepted diagnostic criteria for HE. Diagnosis relies on the clinical presentation of CNS symptoms and anti-thyroid antibodies, but when thyroid function is checked, most of the patients are euthyroid. [8,9,] Anti-NMDR encephalitis is frequently misdiagnosed as Hashimoto encephalopathy, so patients with previous Hashimoto encephalopathy who aren't responding to the supportive treatment should be checked for antibodies. Overall, HE is a rare, progressive and relapsing disease, that needs to be explored more to better understand the mechanism and further management.

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407. Rapidly Progressive Neuromyelitis Optica Spectrum Disorder

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Background: Neuromyelitis Optica Spectrum Disorder (NMOSD) has a polyphasic course in 90-95% of cases. Mortality ranges from 9 to 32% worldwide, rates are higher among African American populations. The mean disease duration at time of death is 6.9-8.2 years. Death from a rapidly progressive course within months of onset is atypical. We present a case of rapidly progressive NMOSD despite treatment.

Case: 36-year-old African American man with systemic lupus erythematosus (SLE), venous thrombosis and latent tuberculosis had a 3-year progressive neurological course with intractable nausea, bilateral optic neuritis, and longitudinally extensive transverse myelitis. He met diagnostic criteria for AQP4-IgG-seropositive NMOSD. Over the course of 3-years he was treated with methylprednisolone, plasma exchange (PLEX), and Rituximab. Despite multiple immunomodulatory therapies his disease and disability progressed rapidly. He was admitted to Neuro-ICU with acute hypoxic respiratory failure and global cerebral dysfunction. Work-up was negative for toxic-metabolic causes, nutritional deficiencies, and bacterial, viral, fungal or mycobacterial CNS infections. CSF studies were remarkable for mild granulocytic pleocytosis, mildly elevated protein (52) and glucose (81), normal IgG index, elevated myelin basic protein (>528) and AQP4 FACS titer of 1:256. He received PLEX with no improvement. His initial MRI showed T2-hyperintensities within periventricular and supratentorial subcortical white matter, medulla and throughout cervical-thoracic spine. Repeat MRI showed evolution of medullary lesion, new areas of extensive edema within the pons, midbrain and both hemispheres, ventriculomegaly, diffuse cortical and deep gray matter diffusion restriction and supratentorial leptomeningeal enhancement. Despite aggressive medical management, he developed worsening hydrocephalus, herniation and death.

Conclusion: NMOSD may present with an aggressive and rapidly progressive course. Mortality rate of NMOSD and SLE is higher in African-Americans, and combination of both may predispose to a fulminant disease progression. Co-occurrence of these conditions and long-term immunosuppression makes diagnosis and management challenging.

408. $Ca_V\alpha2\delta$ Autoimmune Encephalitis: A Novel Antibody and Its Characteristics

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Objective: Discovering novel antibody enables diagnosis and early treatment of the autoimmune encephalitis. We discovered a novel antibody targeting a synaptic receptor and characterized the pathogenic mechanism.

Method: We screened for unknown antibodies in serum and CSF samples from patients who underwent antibody tests for autoimmune encephalitis. Samples with reactivity to rat brain sections and no reactivity to conventional antibody tests underwent further process for antibody discovery, using immunoprecipitation to primary neuronal cells, mass-spectrometry analysis, antigen-binding assay on antigen-overexpressed cell line, and electrophysiology assay with cultured hippocampal neurons.

Results: Total 4,735 patients were screened, and 62 patients had an operationally defined 'unknown antibody' (immunoreactivity to rat brain sections without a known conventional antibody). Finally, two patients had a novel antibody against CaV$\alpha2\delta$ (voltage-gated calcium channel alpha-2/delta subunit). The patient samples stained neuropils

of the hippocampus, basal ganglia, and cortex in rat brain sections and bound to a CaVα2δ-overexpressing cell line. The patients were associated with preceding meningitis or neuroendocrine carcinoma. Both patients responded to immunotherapy. In cultured neurons, the antibody reduced neurotransmitter release from the presynaptic nerve terminals and decreased both excitatory postsynaptic currents (EPSCs) and inhibitory postsynaptic currents (IPSCs), by interfering with tight coupling of calcium channels and exocytosis.

Interpretation: Here, we found a novel autoimmune encephalitis associated with anti-CaVα2δ antibody. Further analysis of the antibody in autoimmune encephalitis might promote the early diagnosis and treatment.

409. Genetics of Anti-NMDAR Encephalitis Implicates Natural Killer Cells

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Paraneoplastic syndromes such as the anti-NMDAR encephalitis, where CSF autoantibodies against NMDAR are prevalent have been recently discovered, manifesting with psychiatric symptoms, abnormal behavior, seizures and dysautonomia. These were initially reported in association with ovarian teratoma(25%), but also found in many cases without tumors(75%). Teratomas associated with this syndrome typically contain CNS-like tissue, suggesting immunity toward the tumor as an important trigger. We conducted the world's first multi-ethnic genome wide association (GWA) screen using SNP arrays in a discovery cohort of anti-NMDAR cases (n=306) and ethnically matched controls (n=4449), replicating top associations in a validation cohort of 164 cases and 955 controls. Genetic principle components along with demographic variables, were used as covariates in additive linear models. Replicated GWA effects were validated by taqman assays in 35 anti-NMDAR cases and 356 ethnically matched controls. Analysis revealed 4 GWA significant genetic loci mapping to ACP2, immunoglobulin IGHG3, DMXL2, and KIR genes ($p<5x10^{-8}$) in the discovery cohort with replication ($p<0.05$) in a validation cohort. Effects in the HLA region were surprisingly absent. Taqman based assays were conducted on a third independent cohort of anti-NMDAR cases, and KIR and ACP2 replicated in accordance with their effect size. In the KIR loci, the highest signals mapped to KIR3DL1 gene represented by rs607149 (discovery $p=6.4x10^{-12}$;OR=2.7, replication $p=2.4x10^{-6}$; OR=2.0) and rs142023169 (discovery $p=2.7x10^{-8}$;OR=2.2, replication $p=4.2x10^{-4}$;OR=1.8). Our analysis reveals novel genetic effects in anti-NMDAR encephalitis including effects in immunoglobulin genes, and one of the strongest KIR associations ever observed today. Our analysis supports the role of NK cells and KIR receptors in anti-NMDAR encephalitis pathogenesis.

410. Optical Coherence Tomography Demonstrates Occult Optic Neuropathy in Neurosarcoidosis

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Objective: To 1) evaluate whether retinal layer thicknesses differ in a large cohort of patients with neurosarcoidosis (NS) as compared to healthy controls (HCs), and 2) examine retinal layer thickness abnormalities according to NS phenotypes and global disability levels.

Background: Clinically-evident optic neuropathy is a known manifestation in NS and can be characterized using optical coherence tomography (OCT). However, the presence and clinical significance of occult optic neuropathy in patients with NS - a disorder with diverse clinical phenotypes - remains largely unexplored.

Methods: In this cross-sectional study, 88 patients with NS (176 eyes; 38 with history of clinically-evident optic neuropathy [NS-ON] and 144 without a history of clinically-evident optic neuropathy [NS-NON]) and 83 age-, race- and sex-matched healthy controls (HC) underwent spectral-domain OCT assessment. Patients with a history of other ophthalmological disorders, including intraocular sarcoidosis, were excluded. Statistical analyses were performed using mixed-effects linear regression models, accounting for within-subject inter-eye correlations.

Results: Mean ganglion cell + inner plexiform layer (GCIPL) thickness was reduced in both NS-ON eyes (64.6±11.4μm) and NS-NON eyes (73.2±6.5μm) as compared to HC eyes (75.3±8.8μm; $p<0.001$ and $p=0.004$, respectively). Furthermore, GCIPL thickness was significantly reduced in NS-ON versus NS-NON eyes ($p<0.001$). Mean peripapillary retinal nerve fiber layer (pRNFL) thickness was lower in NS-ON eyes (77.3 μm±15.8μm) versus NS-NON eyes (92.9±11.7μm; $p<0.001$) and HC eyes (93.3±9.6μm; $p<0.001$). Examining NS phenotypes, GCIPL thickness was reduced in patients with involvement of any cranial nerves (even after excluding NS-ON eyes) as compared to patients without cranial nerve involvement ($p=0.02$). Finally, lower GCIPL thickness was associated with higher levels of global disability as measured by the modified Rankin Score (p=0.02, 95% CI -6.4 to -0.5).

Conclusions: Patients with NS exhibit lower GCIPL and pRNFL thicknesses as compared to HCs. Furthermore, GCIPL thickness - a sensitive marker of retinal neuro-axonal loss - is reduced even in NS eyes without a history of clinically-evident optic neuropathy. Our findings suggest that occult optic neuropathy occurs in NS and may act as a marker of widespread central nervous system degeneration, as

greater reductions in GCIPL thickness were associated with worse clinical outcomes.

411. Longitudinal Analysis of Cortical Demyelination in Multiple Sclerosis (MS) Using Multimodal High-Resolution 7T MRI

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Background: Cortical lesions are common and often extensive in MS. Quantifying the impact of cortical lesions on clinical disability, and of disease-modifying treatment on cortical lesion development and evolution, have been limited due to difficulty visualizing cortical lesions in vivo. We have recently demonstrated that combining T2*-weighted (T2*w) and T1-weighted Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) MRI at 7T dramatically improves cortical lesion visualization.

Objective: We longitudinally characterized cortical lesions and assessed their relationship with clinical and other MRI characteristics.

Methods: We enrolled 64 adults with MS (44 relapsing remitting (70%), 15 secondary progressive (24%), 4 primary progressive (6%)), who underwent 7T brain MRI (T2*w and MP2RAGE, each with 0.5mm isometric resolution), 3T brain and spine MRI, and clinical evaluation annually for 1 year. Cortical lesions were segmented manually on 7T images and categorized as leukocortical, intracortical, or subpial. White matter and spinal cord lesion burden were also determined.

Results: At baseline, 94% of individuals (60/64) had ≥1 cortical lesion. Median cortical lesion number was higher in progressive MS (median 56, interquartile range (IQR) 91, range 2-203) than relapsing MS (median 15, IQR 28, range 0-168; $p<0.01$). Cortical lesion number correlated with physical and cognitive measures of disability. There was a weak correlation between subpial and white matter lesion volume ($r=0.37$, $p<0.001$). 53 individuals completed 1 year of follow-up, of whom 12 (8 relapsing, 4 secondary progressive) developed ≥1 new cortical lesion. 5/12 people with new cortical lesions were on highly effective disease-modifying therapy during the follow up period.

Conclusions: Using sensitive 7T MRI techniques, cortical lesions are detected in almost all MS cases. Cortical lesions are associated with worse and progressive disability. Current disease-modifying therapies may not be effective at stopping cortical lesion formation.

412. Autoimmunity to Hypocretin/Orexin and Molecular Mimicry to Flu in Type 1 Narcolepsy

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Background: Type 1 narcolepsy (T1N) is caused by a hypocretin (HCRT/orexin) cell loss. Association with DQB1*06:02/DQA1*01:02 (DQ0602, 98% vs. 25%), T cell receptors (TCR) and other loci indicate autoimmunity. Onset is seasonal and associated with influenza-A, notably pandemic 2009H1N1 (pH1N1) infection and the pH1N1 vaccine Pandemrix®. The strong HLA association and unique effects in TCR αβ suggest that autoantigen presentation by DQ0602 to CD4+ T cell is crucial. We surveyed CD4+ T cell binding to autoantigens and flu antigens presented by DQ0602 in narcolepsy versus controls, identifying the immunological basis of narcolepsy.

Methods: Higher tetramer-peptide specific $CD4^+$ T cells was found with $HCRT_{54\text{-}66\text{-}NH2}$, $pHA_{273\text{-}287}$ and $NP_{17\text{-}31}$ in 77 T1N than that in 44 DQ0602 controls. Single cell TCR sequencing after FACS sorting was conducted and more than 600 TCR clones transfected into Jurkat 76 cells to test for activation after peptide presentation by RM3-DQ0602 cells. Crystallography of specific TCR clones presentation by DQ0602-$HCRT_{54\text{-}66\text{-}NH2}$, $pHA_{273\text{-}287}$ and $NP_{17\text{-}31}$ was conducted to investigate molecular mimicry. Furthermore, phenotyping of dextramer-DQ0602 positive CD4+ T cells both in vivo and vitro was performed by unbiased 10X genomics.

Results: Most TCR clones from separate population of tetramer DQ0602-antigen positive CD4+ T cells were activated by peptides presented by antigen presenting cells. TCR clones of TRAV20_CAVQARSWGKLQF_TRAJ24 and TRBV4-2_CASSQGPDSRETQYF_TRBJ2-5 were retrieved using DQ0602-$HCRT_{NH2}$ ($HCRT_{54\text{-}66\text{-}NH2}$ and $HCRT_{86\text{-}97\text{-}NH2}$). Sharing of clones using TRBV4-2 was notable between $HCRT_{NH2}$ and $NP_{17\text{-}31}$ so far as this exact segment is modulated by rs1008599, polymorphism associated with T1N. TRAJ24/TRBV19 were commonly activated by $pHA_{273\text{-}287}$. $NP_{17\text{-}31}$ was involved notably TRAV8-6_TRAJ34/TRBV7-9_TRBJ2-3. Crystallography of TCR presentation together with TCR modeling with activation by $HCRT_{NH2}$, $pHA_{273\text{-}287}$, and $NP_{17\text{-}31}$ and phenotyping of dextramer-DQ0602 CD4+ T cells are coming soon and will be more suggestive to immunity of narcolepsy.

Conclusion: Our results provide strong evidence for autoimmunity and molecular mimicry with flu antigens modulated by genetic components in the pathophysiology of T1N.

413. Improving Accuracy of Myasthenia Gravis Autoantibody Testing by Reflex Algorithm

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Objective: To improve myasthenia gravis (MG) autoantibody testing.

Methods: MG serological tests with confirmatory or refuting clinical-electrodiagnostic (EDX) testing and cancer evaluations were reviewed over 4-years (2012-2015). All patients had acetylcholine-receptor-binding (AChR-Bi), modulating (AChR-Mo) and striational (STR) autoantibody testing, and negatives reflexed to muscle-specific-kinase (MuSK). Thymoma and cancer occurrences were correlated with STR and reflexed glutamic-acid-decarboxylase-65 (GAD65), ganglionic-acetylcholine-receptor (alpha-3), collapsin-response-mediating-protein-5 (CRMP5), and voltage-gated-potassium-channel-complex (VGKC) autoantibodies.

Results: Of 433 tested, 133 (31%) met clinical-EDX criteria for MG. Best sensitivity (90%) occurred at AChR-Bi>0.02nmol/L, leaving 14 negative (6-ocular-MG, 7-generalized-MG, 1-MuSK-MG) with specificity 90% (31 false-positives). Using AChR-Mo antibodies (>20% loss) specificity was better (92%, 24 false-positives), however sensitivity dropped (85%). Specificity improved (95%) by testing AChR-Mo when AChR-Bi are positives, resulting in 45% reduction of false-positives (31 to 17), maintaining AChR-Bi 90% sensitivity. Cut-off values recommended by area-under-curve analysis did not outperform this approach. AChR-Bi and AChR-Mo values were significantly higher in true-positives. Computed tomography (CT) evaluations in 121 MG revealed 16 thymomas. Historical or subsequent cancers occurred in 22. STR and reflexed autoantibodies were not more common in MG with thymoma or other cancers. Full-body CT (n=34) was performed in those with STR and reflex autoantibody positivity, but without additional cancers found.

Conclusion: Accuracy of MG serological testing is improved by reflexing AChR-Bi positive cases to AChR-Mo. STR and other reflexed cancer evaluation autoantibodies did not provide value beyond standard CT-chest imaging at the time of MG diagnosis. Diagnostic certainty is informed by AChR-Bi and AChR-Mo with higher values increasing specificity.

414. A Rare Case of Antisynthetase Syndrome Associated Immune Mediated Myopathy in an Adult Male

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Objective: To describe a case of antisynthetase syndrome in an adult male and spread awareness of antisynthetase syndrome associated immune mediated myopathy.

Background: Antisynthetase syndrome is a rare autoimmune condition characterized by antibodies directed against aminoacycl-transfer RNA synthetases, of which anti-Jo-1 is the most common associated antibody. Core clinical characteristics include interstitial lung disease, inflammatory myopathy, and inflammatory polyarthritis. Associated symptoms include fever, Raynaud's phenomenon, and mechanic's hands. These symptoms usually respond to immunosuppressive therapy.

Case Description: A 45-year-old man presented with 4 week history of fever, night sweats, weight loss, diffuse joint pain and swelling, dyspnea, cough, and progressive proximal weakness. He was previously treated with prednisone for one year prior to admission for presumed rheumatoid arthritis. Prednisone was stopped approximately two months prior to symptom onset. General examination showed diffuse joint swelling and tenderness of the ankles, knees, wrists, metacarpophalangeal, and interphalangeal joints bilaterally. Neurological examination demonstrated mildly asymmetric weakness of the left more than right, proximal more than distal upper and lower extremities. Serological testing revealed elevated ESR, CK, aldolase, and markedly elevated anti-Jo-1 antibodies and aminoacycly-transfer RNA synthetases. CT chest revealed patchy consolidations, pulmonary micronodules, and mediastinal and hilar lymphadenopathy concerning for interstitial lung disease. Pelvic MRI showed increased STIR signal mainly in the lumbar paraspinal muscles, gluteus muscles, adductor muscles, and iliopsoas suggestive of myositis. Electromyography(EMG) demonstrated electrodiagnostic evidence of a diffuse irritable myopathy. Biopsy of the left deltoid following initiation of methylprednisolone and mycophenolate mofetil showed minimal fiber size variation and patchy upregulation of MHC-1 without evidence of inflammation. Given positive anti-Jo-1 antibody with evidence of inflammatory myopathy, inflammatory polyarthritis, and interstitial lung disease, the diagnosis of antisynthetase syndrome was made. The patient was treated with prednisone, mycophenolate mofetil, and IVIG with partial improvement of weakness, dyspnea, and arthralgia on follow up one month later.

Conclusion: Antisynthetase syndrome should always be considered in patients presenting with acute to subacute onset of myopathy and interstitial lung disease, especially if the presentation also includes polyarthritis. Anti-Jo-1 antibody is the most common antibody associated with antisynthetase syndrome. There is a wide spectrum of disease severity, making early diagnosis of this disease difficult, particularly if the patient's findings are mild. Furthermore, patients with antisynthetase syndrome may experience relapses and progression of symptoms with time. Thus, close clinical monitoring and appropriate treatment of these patients is needed.

415. Longitudinally Extensive Transverse Myelitis: A Rare Neuromyelitis Optica Spectrum Disorder

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Case Report: 57 y/o AAF with past medical history of HTN and polysubstance abuse presented with two weeks of progressive bilateral lower extremity weakness. Motor exam was normal in the upper extremities but only 2/5 in her lower extremities. Reflexes were 2+ in the arms but brisk bilaterally in the patellar and ankles. Babinski was equivocal. MRI of the cervical, thoracic and lumbar spine w/wo contrast showed extensive cord edema involving the cervical thoracic cord. MRI brain w/wo contrast was unremarkable. Lumbar puncture revealed pleocytosis with total WBC of 700 with 84% lymphocytes. CSF protein was increased to 105 mg/dl. Serum

NMO IgG antibody titer was 270.1 U/ml. Patient was prescribed 1-gram intravenous Solu-Medrol per day for 5 days followed by azathioprine maintenance therapy. Over the next two weeks, the weakness improved significantly, and she was discharged to rehab.

Discussion: Longitudinally extensive transverse myelitis is defined as spinal cord inflammation that extends over three or more vertebral spinal cord sections. It is associated with NMO and rarely with multiple sclerosis. Presence of NMO-IgG antibodies confirms NMO spectrum disorder. Symptoms may include paraparesis or quadriparesis with bowel, bladder incontinence and gait disturbances. Treatment options include high dose corticosteroids and plasmapheresis for the acute phase and maintenance immunotherapy. This case is notable for the patient's classic symptoms, extreme lesion length, the high NMO titer, and the patient's impressive response to treatment.

416. Neuronal Septin Autoimmunity: Differentiated Serological Profiles & Clinical Findings

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Background: Septins are pan-eukaryotic GTP-binding proteins. They form hetero-oligomeric structures imparting cellular scaffold and diffusion barrier functions. Neuronal septins-5 and -7 have structural diversity (complexed with septin-6 and 11, among others). Purported functions include regulation of neurotransmitter exocytosis (septin-5), and dendritic branching and cytokinesis (septin-7). We previously reported septin-5-IgG antibody as biomarker of autoimmune cerebellar ataxia. We report our comprehensive neuronal septin complex autoimmunity experience.

Methods: Patients were all 17 with subacute neurological illnesses (1997-2020) whose serums (16) or CSF specimens (9) underwent clinical evaluation for neural antibodies, and fulfilled mouse tissue-based indirect immunofluorescence IgG 'septin pattern' criteria (staining of diffuse neural synapses [cerebrum- and cerebellar molecular layer-predominant] and renal glomeruli). Septin specificities (5, 6, 7, and 11) were confirmed molecularly (using ≥1 of recombinant protein western blots, and GFP-septin transfected fixed HEK293 cell-based assays [CBAs]). Four CSF specimens were evaluated for cell surface IgG binding. Clinical data, including responses to ≥1 of corticosteroids, IVIg, and plasma exchange are reported.

Results: Septin-5- and -7 blots and CBAs yielded IgGs reactive with septin-7 (11 patients), septin-5 (4), or both (2). Supportive of IgG pathogenicity, all 4 CSF specimens were reactive with extracellular-facing plasma membrane surfaces of live hippocampal neurons. Nine of 17 patients were men. Median symptom onset age was 62 years (range, 40-85). Six patients with pancerebellar ataxia, with eye movement disorders prominent, accounted for all septin-5-IgG seropositive cases (2 had septin-7-IgG coexisting on CBA and blot). None had neoplasms reported. Outcomes available in 4 were: improvements with immunotherapy (2), spontaneous improvement (1), and death (1). The remaining 11 patients were septin-7-IgG seropositive on CBA and blot; 6 of 7 serums tested also yielded coexisting septin-6- and -11-IgGs on blot. Neurological phenotypes were encephalopathy (3, relapsing in 2), myelopathy (3), encephalomyelopathy (2), painful myelopolyradiculopathy (2) and episodic ataxia with normal exam (1). Psychiatric symptoms (≥1 of agitation, apathy, catatonia, disorganized thinking, and paranoia) were prominent in 3 of 5 with encephalopathic symptoms. Four had ≥1 neoplasm (breast adenocarcinoma, 2; non-Hodgkin lymphoma, 1; carcinoid, 1; myelodysplastic syndrome, 1), one of whom had a prolonged but resolving encephalopathy post-HSV-1 encephalitis. Outcomes available post-immunotherapy in 4 others were remission (2), improvement (1), and death (1).

Conclusion: Septin-5- and septin-7 neurological autoimmunity patients have contrasting neurological phenotypes, paraneoplastic association and IgG profiles, though are unified by pathogenic IgG potential and treatment response.

417. Rare Case of Immunotherapy Refractory Fatal Neuromyelitis Optica Syndrome Related Encephalitis

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Introduction: Neuromyelitis Optica spectrum disorders (NMOSD) are a group of autoimmune demyelinating conditions of the optic nerve, spinal cord and brainstem. Serum anti-Aquaporin-4 receptor antibodies help confirm this diagnosis [1]. NMOSD usually responds to immunosuppressive therapy and it can have rare supratentorial brain involvement. Here we present a case of fatal acute encephalitis due to NMOSD that was unresponsive to standard immunosuppressive therapy [2].

Case Report: We present a case of a 36 years old African-American gentleman with prior history of systemic lupus erythematosus, rheumatoid arthritis, lupus nephritis and gastro-esophageal reflux disease. He was diagnosed with neuromyelitis optica 5 weeks prior to admission following bilateral visual impairment and was treated with 2 sessions of intravenous (IV) rituximab subsequently. He presented with progressive paraparesis and urinary retention of 3 days duration. MRI revealed new T2 FLAIR hyperintensities in cervical spine, with scattered supratentorial deep white matter T2 hyperintense lesions. He needed endotracheal intubation secondary to bulbar weakness on day 4 post-admission. The serological and cerebrospinal fluid studies ruled out any new

acute infective, autoimmune or paraneoplastic etiology (other than Aquaporin antibodies that were positive again). He was treated with plasma exchange (total 5 alternate day sessions), that were started on day 5 post-admission, followed by IV steroids. His hospital course was complicated by segmental pulmonary embolism and asymptomatic anemia, both treated appropriately. On day 14, he underwent tracheostomy and percutaneous endoscopic gastrostomy placement, due to persistent bulbar weakness. On day 17 postadmission, he developed sudden onset acute encephalopathy with diabetes insipidus. Repeat MRI brain showed extensive vasogenic edema involving periventricular white matter and brainstem including pons and medulla, with restricted diffusion in diffuse cortical areas, with communicating hydrocephalus and raised pressure on spinal tap. High-dose IV dexamethasone and IV immunoglobulins, hyperosmolar therapy and ventriculostomy placement were started. The family, who had been updated regularly throughout his course, decided to change his Code status to "Do not resuscitate" on day 16. He continued to deteriorate with progressive brainstem reflex loss despite aggressive medical management. He unfortunately died after suffering cardiorespiratory arrest on day 18.

Conclusion: NMOSD encephalitis is not an uncommon entity within the NMO spectrum disorders. It is usually responsive to immunosuppressive therapy. However, our case highlights the need to be vigilant about aggressive course of NMOSD encephalitis, that can progress rapidly despite standard immunosuppressive therapy.

418. Assessing Diagnostic Accuracy of Multiple Sclerosis: A Quantitative Survey of Neurology Residents at an Academic Institution

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Background: Multiple sclerosis (MS) is an immune mediated disorder affecting the central nervous system with a potential to result in significant disability if therapeutic intervention is delayed. The global prevalence of MS is more than 2.3 million. While MS is associated with a typical pattern of lesions on brain imaging cerebrospinal fluid (CSF) analysis can help clarify the diagnosis. Several CSF markers have been associated with a diagnosis of MS including intrathecal IgG synthesis rate, oligoclonal bands, IgG index and protein count. The methods applied in sample procurement and analysis of CSF are also essential in accurate diagnosis of multiple sclerosis. PURPOSE: To assess the understanding of appropriate CSF sample procurement and CSF markers essential in definite diagnosis of MS, among Neurology residents at a major university medical center.

Methods: A confidential online survey was emailed to all Adult and Child Neurology residents in our program. The survey consisted of 10 questions addressing CSF sample procurement and CSF markers essential for MS diagnosis. Periodic email reminders were sent to residents to facilitate maximal response rate. Responses were kept anonymous and subjected to analysis.

Results: 16 Neurology residents completed the online survey, a 55% overall response rate. The percentage response rates varied among different levels as follows: PGY1-50%, PGY2-33%, PGY3-70% and PGY4-100%. The Analysis of resident responses for each of the questions confirmed an overall accuracy of 40%.

Conclusion: In our quantitative survey of Adult and Child Neurology residents at our institute, the diagnostic accuracy in assessing for multiple sclerosis using CSF studies is lower than expected. We also felt that the lack of knowledge was also responsible for the lower response rate. The above findings suggest that there is utility of further resident training on CSF markers in MS to improve knowledge. We intend to implement a series of didactics on CSF analysis in MS diagnosis in our institution to address the knowledge gap among Neurology residents.

419. Anti-Amphiphysin Positive Partial Stiff Person Syndrome in an Elderly Woman with a Breast Mass

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Background: Stiff-person syndrome (SPS) is a rare autoimmune disorder characterized by progressive muscle stiffness and painful muscle spasms, classically associated with anti-glutamic acid decarboxylase (GAD). Here we present an unusual case of partial SPS with positive anti-amphiphysin antibody in an elderly woman with a breast mass.

Case Presentation: 83-year-old white female with PMHx of HTN, celiac disease, history of breast lump for several years, who presented with bilateral lower extremity weakness and painful spasms for 3 months, worsening over 2 weeks. Upon presentation, patient had spastic paraplegia (L>R) and was wheelchair bound. She had dystonic inversion of the left ankle with redness and swelling. Babinski sign showed extensor plantar response bilaterally. She had multiple intermittent painful spasms in lower extremities triggered by tactile stimuli. Breast exam showed 5.5x6.6 hard palpable mass.MRI brain/C/T/L spine and lumbosacral plexus were unremarkable. LP revealed elevated protein (WBC 6, RBC 53, Protein 66, glucose 52). EMG showed sensorimotor axonal polyneuropathy in lower extremities, as well as spontaneous ongoing muscle activity at rest and co-activation of agonists and antagonist muscles in lower extremities and right upper extremity, which indicated a central process like stiff person syndrome. Valium helped to relieve the painful spasm. She was treated with plasma exchange. Amphiphysin antibody returned as positive while anti-GAD antibody was negative. Breast mass biopsy revealed invasive ductal carcinoma, ER/PR positive Her2 negative, Stage IIIC. Oncology recommended anastrozole, and further treatment as outpatient.

Discussion: This case demonstrates an extremely rare form of partial stiff-person syndrome (SPS), in an elderly woman who presented with stiff-limb syndrome and was found to have positive amphiphysin antibody and invasive ductal carcinoma of the breast. With the spastic paraplegia and bilateral extensor plantar response pointing to a central process,

further research is needed toward the understanding the pathophysiology and treatment options.

420. Covid-19 Presenting as Post-Infectious Myelitis: A Case Report

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Introduction: COVID-19 has been shown to have neurological presentations and neuro-invasive potential. However, its effect on the spinal cord has not been reported or investigated.

Methods: Case report.

Results: A 72-year-old woman presented to an outside hospital with subacute profound right leg weakness and urinary retention. Past medical history was significant for hypertension and resected ovarian cancer that had presumably remained in remission. She had no history of autoimmune or rheumatological conditions. MRI spine revealed patchy FLAIR lesions in the C3-T1 area with faint enhancement felt to be incidental at outside hospital. MRI brain was unremarkable. Nasopharyngeal swab performed prior to discharge to skilled nursing facility was positive for COVID-19. She came to our hospital from SNF once she began to develop right hand weakness. MRI spine showed slight progression in the previous captured lesions. Cerebrospinal fluids (CSF) studies showed normal profile with negative oligoclonal bands, and elevated myelin basic protein. CSF cytology was negative. CSF viral studies were negative. CT chest revealed bilateral pulmonary peripheral opacities and no evidence for malignancy. Serum studies revealed no evidence of autoimmune or vitamin deficiencies. Given the time course, and that the workup was largely negative aside from a positive COVID-19, we believe that coronavirus was the likely cause of the myelitis or a trigger for a post-infectious process. Since she had no active signs of infection myelitis was treated with IV methylprednisolone and IVIG, after which the patient exhibited mild improvement.

Conclusion: This case report provides more insight into potentially larger neuro-invasive potential of COVID 19. Clinicians should consider COVID-19 on the differential diagnosis of patients presenting with acute/subacute spinal cord syndrome.

421. Pembrolizumab-Induced Myositis and Encephalitis with Bi-Thalamic Involvement Responsive to Rituximab

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Introduction: The emergence of immune checkpoint inhibitors for cancer treatment has introduced novel neurologic immune-related adverse events (ir-AE), which are highly variable in presentation and can cause profound morbidity and mortality. Encephalitis and myositis are well-known complications, although combined cases have rarely been reported.

Objective: To present a case of combined myositis and encephalitis secondary to pembrolizumab monotherapy.

Methods: Case report and literature review

Case: A 68-year-old man with a history of CAD and stage IIIA Merkel cell carcinoma status post excision and radiation therapy presented with fevers, mental status changes and seizures four weeks after starting pembrolizumab monotherapy. On initial examination, the patient was stuporous, with arousal only to vigorous noxious stimuli and then rapidly declined to a comatose state within 48 hours. EEG showed moderate to severe encephalopathy. CSF showed an elevated protein (372) and pleocytosis (103 in tube 1, 66 in tube 4). MRI brain demonstrated multiple foci of T2/FLAIR hyperintensity most notably in the bilateral paramedian thalami, pons, and midbrain without contrast enhancement. He was started on high dose IV methylprednisolone with some improvement in mental status, although he waxed and waned, and was minimally interactive. His course was complicated by the development of rhabdomyolysis with peak CK of 39728 U/L and a severe subacute irritative myopathy on EMG. He received two courses of IVIG in weeks 4 and 6 of his hospitalization with no clinical change. Despite normalization of the CK, he remained profoundly weak in his extremities with only minimal distal activation. He was eventually given 2 weekly doses of Rituximab 750 mg starting week 8 with marked improvement in his weakness and mental status. During his hospitalization, he developed multisystem immune-related complications, including colitis, thrombocytopenia, and granulomatous skin manifestations in addition to numerous infections.

Conclusion: This case demonstrates the profound neurological complications that can arise from checkpoint inhibitor therapy. Our case is unusual given the presence of combined myositis and encephalitis and the rapid decline into a comatose state, which may have been due to the bi-thalamic involvement. In addition, severe neurologic ir-AE including combined CNS and PNS cases are more commonly seen with CTLA-4 or CTLA-4/PD-1 inhibitor therapy whereas our patient was on PD-1 monotherapy. Finally, given our patient's improvement with rituximab, our case suggests that early use of rituximab may be helpful for cases of combined encephalitis and myositis.

422. A Rare Case of Miller Fisher Syndrome Presenting with Hypoglossal Nerve Palsy

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Background: Miller Fisher syndrome (MFS) is a rare variant of Guillain Barre Syndrome (GBS), characterized by ophthalmoplegia, ataxia and areflexia. Cranial nerve involvement can be seen in GBS but rarely in MFS.

Case Presentation: A 32-year-old African American male was admitted to the hospital for 5 day history of dysphagia, dysphonia and dysarthria. Patient then experienced double vision, bilateral hand numbness and right upper extremity weakness. He had an episode of upper respiratory tract infection one week prior to symptom onset. Neurological

examination revealed bilateral abducens nerve palsy, diminished gag reflex, tongue deviation to the right side, decreased sensation more on left arm and leg without proximal-distal difference, right upper limb distal more than proximal weakness, ataxic gait and bilateral (left more than right) dysmetria. Deep tendon reflexes were normal on upper extremities but absent in both knees and ankles. MRI Brain with and without contrast was unremarkable. CSF studies showed normal cell counts and protein. Electromyography/ Nerve conduction velocity testing demonstrated demyelinating changes with prolonged F waves and distal latency with temporal dispersion. Serum GQ1B antibodies IgG/IgM were elevated at 371 IV (reference: 0-50). The diagnosis of MFS was made, and patient was treated with intravenous immunoglobulin for five consecutive days with complete resolution of his symptoms.

Conclusion: MFS is a rare variant of GBS. Cranial nerves (CN) commonly involved in GBS/MFS are III-VI, VII and X. Involvement of CN XII is extremely rare, usually accounts for less than 5% of GBS cases. To our knowledge, the case we presented here is the first case of MFS with unilateral hypoglossal nerve palsy. In a patient presenting with multiple cranial nerve involvement, careful neuro exam should be done with the consideration of GBS/MFS in mind since they respond well to treatment if administrated in a timely fashion.

423. Behcet's Disease Presenting with Intracranial Hypertension Secondary to Superior Vena Cava Thrombosis Successfully Treated with Thrombectomy

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Behcet's disease (BD) is a rare inflammatory autoimmune disorder, known to present with recurrent oral and genital ulcers, uveitis and other systemic manifestations. Neurologic manifestations of BD that have been reported include meningoencephalitis, cerebral venous thrombosis, intracranial hypertension (ICH) and cranial nerve palsies. Involvement of the superior vena cava (SVC) is rare, however should be considered in patients with BD with suspected ICH. Herein, we present a case of a 32-year-old man presenting with ICH as the initial manifestation of BD. He presented with a one-week history of face and neck swelling, headache and blurry vision and after a few days, fever, sore throat and mouth blisters. Lumbar puncture (LP) was performed with opening pressure greater than 50 mm Hg, and closing pressure of 36 mm Hg. CT chest identified thrombosis of SVC extending into the brachiocephalic veins. Work-up revealed elevated inflammatory markers, dilated cardiomyopathy and a family history of BD (cousin), and patient admitted to previous history of genital ulcers. The patient underwent a thrombectomy and was treated with prednisone, with resolution of symptoms. This case reflects the importance of considering rare causes of systemic venous thrombosis leading to secondary intracranial hypertension, and potential pitfalls in management.

424. Uncommon Manifestations of Latent HHV-6: An Unusual Case of Acute Onset Dysarthria and Diplopia

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Recently, HHV-6 has become an increasingly well known CNS pathogen, and has been shown to have possible associations with a variety of neurological symptoms and conditions, including multiple sclerosis, post-transplant limbic encephalitis, encephalitis/meningitis in immunocompetent patients, as well as mesial temporal sclerosis. However, rhombencephalitis is not a frequently reported association with HHV-6. Typical and known etiologies of rhombencephalitis can include autoimmune diseases, paraneoplastic syndromes as well as infectious etiologies. The most common reported infectious cause is *Listeria*, with certain viruses such as enterovirus 71 and herpes simplex virus being other common causes. There have also been reported cases of a brain stem encephalitis secondary to a viral etiology due to EBV and HHV-6, although the association between HHV-6 and brainstem involvement is less frequently reported. Here, we will highlight and discuss the current understanding of HHV-6 as a potential CNS pathogen and present an unusual case of a 70-year-old female who had developed acute onset and intermittent diplopia with progressively worsening dysarthria. In addition, she developed subjective right-sided weakness with increased difficulty holding objects in her right hand. MRI brain was notable for a contrast enhancing upper midbrain lesion. An extensive workup during the course of her hospitalization, including infectious, inflammatory, and paraneoplastic etiologies was unrevealing except for detected HHV-6 in the CSF with amplification on PCR.

425. Occult Growing Teratoma as the Cause of Protracted Symptoms in an Anti-NMDA Receptor Encephalitis Patient with Prior Ovarian Teratoma Removal: Implications for Long-Term, Repeated Monitoring and Treatment

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Although anti-NMDA receptor encephalitis (NMDARE) may follow a malignant course in a small portion of patients, the majority of cases are monophasic and many patients recover to return to their daily lives. Especially in cases where an associated teratoma is found early and resected completely, relapses and cumulative deterioration are considered uncommon. We report a case of NMDARE with persistent language and memory symptoms for four years despite early left ovarian teratoma resection and timely and multiple courses of immunomodulatory therapy. The persistent symptoms disappeared promptly after the discovery and resection of a second teratoma in the right ovary. The patient presented with a comatose mental state accompanied by excessive salivation, oromandibular and whole-body dyskinesia, and hypoventilation, leading to suspicion and confirmation of a diagnosis of NMDARE. An ovarian teratoma was found on computed tomography (CT) and removed, after which, the

absence of any remaining teratoma was confirmed by a follow-up abdominopelvic CT. Her treatment included intravenous immunoglobulins, intravenous steroids, rituximab, tocilizumab, interleukin-2, and electroconvulsive therapy. At one year, although she had regained alertness, her fluency was limited to single words. After almost two years of follow-up in the outpatient department, during which she continued to receive immunomodulatory treatment, she finally was able to speak a few words but complained of short-term memory impairment and emotional lability. Four years after her the start of her illness, a sizable teratoma causing left ovarian torsion was discovered in a workup for menstrual irregularity. After the resection of the teratoma, the patient reported a drastic improvement in all her cognitive and mood symptoms that had persisted prior to the surgery, leading her to discontinue all her medications without experiencing any further symptoms. Our case highlights the importance of continued screening for occult teratomas in NMDARE patients with symptoms refractory to timely teratoma removal and optimum treatment. Developing teratomas not present at disease onset may be a source of peripheral antigen presentation for culprit immune cells in NMDARE, and its prompt resection may lead to rapid symptom improvement.

426. Cerebrospinal Fluid Oligoclonal Bands in Anti-NMDA Receptor Encephalitis

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Objectives: Studies suggest that symptoms in anti-NMDA receptor encephalitis (NMDARE) are directly mediated by autoreactive antibody production in the central nervous system. However, initial cerebrospinal fluid (CSF) findings have been shown to correlate poorly with symptom severity and duration in NMDARE. In order to determine whether the CSF oligoclonal bands (OCB) may be associated with NMDARE symptoms, we retrospectively reviewed the records of 16 NMDARE patients.

Methods: We included patients with a confirmed diagnosis of NMDARE who underwent initial CSF evaluation and were followed up for a minimum of 12 months. We collected information on the severity of disease, the duration of hospitalizations and intensive care unit stays, the presence of uncontrolled seizures, and anti-epileptic drug requirement for each patient.

Results: Of 16 confirmed anti-NMDARE patients, 9 had positive CSF OCBs. CSF OCB positivity was associated with a more severe disease at baseline ($p < 0.01$), and a worse final outcome ($p < 0.01$). Patients with positive oligoclonal bands also had longer hospitalizations ($p < 0.01$), and ICU stays ($p < 0.01$). OCB positivity was associated with aggravation of symptoms despite treatment within 4 weeks ($p = 0.03$). Other CSF indices such as CSF leukocyte count or the immunoglobulin G index were not associated with disease severity, duration, or outcome.

Conclusions: Our results suggest that testing for CSF OCBs at disease onset may be of use in the assessment of disease severity in NMDARE. CSF OCBs may reflect ongoing autoimmune activation better than other conventional CSF findings. Further testing of CSF OCBs for their immune targets may reveal further informative insights.

427. Subacute Encephalopathy and New-Onset Seizures in Autoimmune CASPR2-Antibody Encephalitis with Phenotypical Similarities to Creutzfeldt-Jakob Disease

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Objective: This case report highlights the first report of subacute encephalopathy and seizures in autoimmune CASPR2-antibody encephalitis with phenotypical similarities to Creutzfeldt-Jakob disease at initial presentation. Design/Methods: Case report and literature review.

Background: Autoimmune encephalitis shared similar presentations with CJD but it is a potentially treatable disease with aggressive immunomodulating therapy. It is worthwhile to consider autoimmune encephalitis even in typical CJD cases with positive CJD -related laboratory and diagnostic biomarkers.

Results: A gentleman in his fifties presented to the hospital with subacute severe encephalopathy and new onset seizures with frequent right sided limb twitches. Continuous video electroencephalogram (EEG showed frequent left sided lateralizing periodic discharges (LPDs). Magnetic resonance imaging (MRI) scan of the brain showed mild cortical restricted diffusion (cortical ribboning) and fluid attenuated inversion recovery (FLAIR) hyperintensity, most pronounced in the left parieto-occipital and inferomedial frontal regions. Cerebral spinal fluid analysis showed negative infectious markers and positive 14-3-3 and Tau proteins, which raised concerns of CJD. Autoimmune encephalitis panel was sent and showed positive anti-CASPR2 IgG antibody. Patient received intravenous methylprednisolone and plasmapheresis given concerns of autoimmune encephalitis. Patient showed interval improvement in MRI findings with resolution of restricted diffusion and continuous EEG showed resolution of LPDs. 4 weeks post plasmapheresis, his mental status showed significant improvement and seizures stopped.

Conclusions: Our case discusses the challenges of diagnosing autoimmune encephalitis in a case with phenotypical similarities to Creutzfeldt-Jakob disease. This case shared common typical biomarkers to support a diagnosis of CJD including positive 14-3-3 and Tau protein in CSF, periodic sharp wave complexes in EEG and cortical restricted diffusion in MRI findings. Aggressive immunosuppression was started after that an extensive autoimmune encephalitis panel showed positive anti-CASPR2 IgG. The positive antibody and significant clinical improvement post plasmapheresis point towards the diagnosis of anti-CASPR2 encephalitis.

428. Anti-Myelin Oligodendrocyte Glycoprotein (MOG) Antibody-Associated Bilateral Optic Neuritis: To Treat or Not to Treat?

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Objective: In this report, we present a case of bilateral optic neuritis (ON) associated with anti-Myelin Oligodendrocyte Glycoprotein (MOG) Antibody. It is an antibody mediated demyelinating disease of the central nervous system (CNS) that is a distinct entity from other demyelinating processes of the CNS, and its prognosis and the role of chronic immunomodulating therapy are still uncertain.

Case Report: A 25-year-old African American male with a history of recurrent meningioma presented with a 3-day history of progressive left eye visual loss with painful eye movements, which gradually involved the right eye. Patient had a resection of the meningioma 3 days prior to symptom onset. On exam patient was only able to count finger in both eyes. He could not identify colors and had bilateral grade 2 optic disc edema. MRI brain with and without contrast found bilateral optic nerve enhancement and T2 hyperintense signal. Lumbar puncture revealed elevated opening pressure of 35 cmH20, likely due to the meningioma, negative for infection (WBC: 4, RBC: 6, protein: 52, glucose: 47) and negative oligoclonal bands. Serum MOG antibodies were positive to a titer of 1:40. NMO was negative. The patient was started on pulse dose IV steroids for 3 days and greatly improved and his vision returned to baseline. Chronic immunomodulating therapy was not started upon discharge. Repeat MRI brain 2 months later documented complete resolution of abnormal optic nerve signal and enhancement. Repeat serum MOG antibody titer came down to 1:10. Patient's vision remained at baseline, and when followed over 5 months he did not have any recurrent neurological events.

Discussion: Although considered as a subtype of Neuromyelitis optica spectrum disorders (NMOSD), studies have shown that patients with MOG antibody-associated disorders have fewer attacks, and better recovery than patients with AQP4 antibodies[1]. These patients have had a more favorable outcome and most with a monophasic disease pattern[2,3]. A review of 252 UK patients found that 36% of patients diagnosed with MOG-antibody disease relapsed after a median duration of 16 months[4]. It remains unclear whether patients with MOG antibody associated NMSOD should be treated with chronic immunomodulating therapy or not. Clinicians must make decisions on a case-by-case basis, taking the individual patient's disease severity, longitudinal antibody seropositivity/seronegativity and patient comorbidities all into account before deciding.

K-578. Effects Of Myocyte Enhancer Factor 2c (mef2c) On Microglia Function

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Microglia are the resident macrophages of the central nervous system, acting as the immune effector cell of the brain and contribute to maintenance of homeostasis. Microglia are developmentally unique, arising from an early yolk sac progenitor and migrating to the developing brain. The microglia cell fate is heavily reliant on other brain cell types and is modulated by a network of environmentally dependent transcription factors, one of which is myocyte enhancer factor 2C (MEF2C). MEF2C has roles in neurodevelopment with loss of one allele leading to MEF2C Haploinsufficiency Syndrome (MHS), a syndromic form of autism. Patients with MHS exhibit a severe autism spectrum disorder characterized by intellectual disability, epilepsy, stereotypical movements, social deficits, and absent speech. Declining MEF2C expression in microglia is implicated in aging related phenotypes. We have shown that MEF2C expression is enriched in microglia when compared with other cell types of the brain throughout human development. We have utilized induced pluripotent stem cells (iPSCs) and the gene editing technology CRISPR (clusters of regularly interspaced short palindromic repeats) to generate isogenic cell lines with single and double allelic knockouts of MEF2C. We have generated stem cell derived microglia from isogenic MEF2C iPSC cell lines and analyzed the structure, function, and transcriptomic effects of loss of MEF2C. Loss of microglial MEF2C results in a more amoeboid morphology with higher lipid droplet content and CD68 staining, characteristic of microglial activation.

Behavioral Neurology

182. Effects of Methylphenidate on Verbal Creativity, Verbal Fluency, and Convergent Thinking Tasks in Adults with Attention-Deficit Hyperactivity Disorder

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A common treatment for the symptoms of attention-deficit/hyperactivity disorder (ADHD) is methylphenidate (MPH), which functions as a norepinephrine-dopamine reuptake inhibitor. Both the dopamine and norepinephrine systems have been shown to impact aspects of creativity. Individuals with ADHD have been shown to perform better on some measures of creativity, and MPH has been shown to increase creativity in people without ADHD. However, it is not clear whether MPH augments or impairs creativity in adults with ADHD. Seventeen participants diagnosed with ADHD, aged 18-40, participated in the study. Participants attended 2 sessions where they took the prescribed amount of MPH prior to the appointment for one session, and another session where they withheld their MPH. Participants were administered a battery of assessments in a counterbalanced fashion, including the Verbal Torrance Test (verbal creativity), convergent thinking tasks (compound remote associates, anagrams), and divergent thinking tasks (semantic and letter fluency). The number of words generated on the semantic fluency task as well as the solution latency for correctly solved

problems were significantly increased for MPH compared to no MPH. Furthermore, MPH significantly increased originality scores on the Verbal Torrance Test, and a trend toward significance was found for the overall Verbal Torrance battery average score. In sum, results from this study suggest that MPH improves performance on semantic fluency but increases response latency on an anagrams task in adults with ADHD. Furthermore, MPH appears to enhance originality in the verbal domain in adults with ADHD. Therefore, MPH appears to improve performance on divergent tasks but impair performance on convergent tasks in individuals with ADHD.

183. Cognitive Impairment and Risk Factors of LATE, a Novel Degenerative Pathology

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Background: Limbic predominant age related TDP-43 encephalopathy (LATE) is a newly proposed term to denote the contribution of transactive response DNA-binding protein of 43 kDa (TDP-43) pathology to dementia at older age. The aim of this work was to study the role of LATE in cognitive impairment and its risk factors in the oldest old (those ≥ 90years old).

Methods: 240 participants of *The 90+ Study* with comprehensive clinical, neuropsychology, and neuropathology data were included. Dementia status, clinical syndrome, and impaired cognitive domains were determined at multidisciplinary post-mortem case conferences blind to autopsy data. Alzheimer's disease neuropathology (ADNP) was defined as CERAD neuritic plaque score≥2 and Braak neurofibrillary tangle stage≥5. We defined LATE as those with at least amygdala and hippocampal TDP-43 pathology (stage>2). We explored the association of LATE and of ADNP with cognition measures by logistic regression analyses adjusting for age, sex, and education. We separately explored the association between medical histories (as potential risk factors) and LATE and ADNP as outcomes adjusting for the above covariates.

Results: 52% of the participants (N=125) died with dementia and of those, 33% were LATE positive (compared to 40% ADNP positive). There was no association between LATE and sex, age at death, or education. Compared with ADNP, LATE was as important a predictor of dementia (OR: 2.9 for ADNP vs. 3.3 for LATE) and clinical diagnosis of Alzheimer's at death (OR: 3.7 for ADNP vs 3.9 for LATE). Both pathologies were significantly associated with impaired memory, language, visuospatial ability, and orientation. Only ADNP (OR=2.1), but not LATE, was associated with impaired executive function. Lower likelihood of LATE was associated with histories of hypertension (but not hypertension medications), cataract, alcohol use (median 1 drink/day), and macular degeneration (trended toward significant association). History of COPD was significantly associated and history of autoimmune conditions (thyroid or rheumatological diseases) trended towards an association with a higher likelihood of LATE. None of the above relationships were seen for ADNP.

Discussion: LATE is an important degenerative pathology in the oldest old comparable to ADNP in its relation to dementia and clinical diagnosis of Alzheimer's dementia. The intriguing associations of LATE with other health conditions warrant further investigation of the potential effect of autoimmunity, reduced brain perfusion, and chronic hypoxia in its development.

184. Do Children with Weakness in Grammar Understanding Have Only Language Deficit?

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Background: Weakness in grammar understanding is key symptom of children with specific language impairments (SLI). The use of term "specific" implies that the deficit is directly and exclusively related to language processes. However, over recent years there have been emerging suggestions of the presence of non-linguistic cognitive difficulties in children with SLI. In our previously research we have revealed that children with deficit in grammar understanding have also weakness in specific cerebral mechanism responsible for simultaneous synthesis [Kiselev, 2017]. If SLI children suffer from the deficit in simultaneous synthesis we can expect the presence of visuospatial impairments in these children. The goal of this research was to examine the hypothesis that children with deficit in grammar understanding have weakness in visuospatial abilities.

Methods: A total of 156 children aged between 5 years 9 months and 6 years 11 months participated in the study. Children were assessed with the task "Comprehension of grammatical structures" from neuropsychological assessment battery. Children were included in the experimental group if they made 50% or more errors on this tasks. Experimental group included 27 children with weakness in grammar understanding (M = 5.47 years, SD = 0.95, 20 boys and 7 girls). Children were included in the control group if they made less than 10% errors. The control group included 27 children. Children from experimental and control group were matched for IQ, gender and age. To assess the visuospatial abilities in children we used 4 subtests from NEPSY (Arrows, Block Construction, Design Copying and Route Finding).

Results: One-way ANOVA by group revealed significant differences (p≤0,05) between the groups for scores in 3 subtests (Block Construction, Design Copying and Route Finding). Children from control group performed better visuospatial tasks in comparison to children with poor grammar understanding.

Conclusions: We have shown that children with deficit in grammar understanding have also weakness in visuospatial functions. According to Luria's hypothesis [Luria, 1976], simultaneous synthesis may play important role in different abilities including visuospatial abilities and grammar understanding. This explanation makes sense in view of idea that there are important parallels between visual perception, especially perception of spatial relations, and speech

understanding. Received results provided insight into cognitive and language mechanisms in typically developing children and the underlying nature of SLI, helping to elucidate the nature of impaired mechanism in children with weakness in grammar understanding.

185. Weakness in Visuospatial Abilities in Children Can Be Caused by Computer Game Addiction

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Background: Over the past two decades, dramatic changes in the environment in which the child develops have occurred. In particular, various digital technologies are increasingly being introduced into the everyday life of children. What kind of specific effect does this new "digital environment" have for development in children? It can be proposed that child who spends a lot of time in the "virtual world" has a risk for delay in the development of basic adaptive mechanisms that we use in "real world", including visuospatial abilities. The goal of this research was to examine the hypothesis that 6-year-old children with computer game addiction have weakness in visuospatial abilities.

Methods: A total of 98 children aged between 5 years 11 months and 6 years 9 months participated in the study. We used questionnaire for parents to reveal children with computer game addiction. According to results of questionnaire children were included in the experimental group that included 26 children with computer game addiction (M = 6.12 years, SD = 0.13, 19 boys and 7 girls). Control group consisted of 26 children without computer game addiction. Children from experimental and control group were matched for IQ, gender and age. To assess the visuospatial abilities in children we have used 4 subtests from NEPSY (Arrows, Block Construction, Design Copying and Route Finding) and the Rey-Osterrieth Complex Figure test.

Results: One-way ANOVA has revealed significant ($p \leq 0{,}05$) differences between groups for scores in 3 subtests from NEPSY (Block Construction, Design Copying and Route Finding) and for amount of spatial mistakes in the Rey-Osterrieth Complex Figure test. Children from control group performed better visuospatial tasks in comparison to children with computer game addiction.

Conclusions: We have shown that children with computer game addiction have weakness in visuospatial abilities. It can be assumed that interaction with real world, including constructive activity, spatial games in the street, sport activity, is a necessary and favorable condition for the development of visuospatial abilities. Children who spends a lot of time playing in virtual world have the disadvantage in such interaction. According to this idea we can assume that computer game addiction can have negative effect on the development of visuospatial functions in children. We are going to perform longitudinal investigation of children with computer game addiction to reveal the influence of this addiction on cognitive development in long-term perspective.

186. Can the Maternal Mindfulness Training during Pregnancy Influence Neurocognitive Development of Offspring?

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Background: There is evidences that maternal anxiety and depression during pregnancy affects child outcomes. It was shown that psychological stress of the pregnant mother is associated with various early negative conditions in the offspring. However, there is lack of studies that have evaluated the effects of maternal psychosocial factors during pregnancy on child neurocognitive outcomes. Can the maternal mindfulness training during pregnancy influence neurocognitive development of offspring? The goal of this research was to evaluate the effect of the maternal mindfulness training during pregnancy on neurocognitive development in 5-6 years old children.

Method: In the current study we included 14 women who participated in six-week maternal mindfulness training during pregnancy. Women were between 14 and 20 weeks gestation. Participants were trained in the practice of mindfulness meditation and its applications to daily life through participation in instructor-led group meditations, lectures about mindfulness practices and discussions. The control group included 14 women who did not participate in this training during pregnancy. When the offspring of the target pregnancies were between 5 to 6 years of age, their neurocognitive development was assessed by Lurias's child neuropsychological assessment battery that is designed to assess five functional domains, including executive abilities, language, memory, sensorimotor and visuospatial abilities. Integral result for every five functional domains was calculated. Children from experimental group consisted of 14 children at 5-6 years of age (M = 5.49 years, SD = 0.99, 9 boys and 5 girls). Children from control group included 14 children (M = 5.61 years, SD = 0.84, 10 boys and 4 girls).

Results: One-way ANOVA has revealed the significant differences ($p \leq 0{,}05$) between groups in one functional domains. Children from the experimental group performed better on subtests from executive functional domains.

Conclusion: We have shown that preschool children whose mothers participated in mindfulness training during pregnancy had better level of executive abilities in comparison to children from control group. These results suggest that maternal mindfulness training during pregnancy may have positive effect on neurocognitive development of children, particularly on the development of executive abilities. However, we need to do further research for revealing the effect mindfulness training on neurocognitive development of children. Particularly, we are going to continue the longitudinal investigation of children from our experimental and control group one year later.

187. Children with Attention Deficit Hyperactivity Disorder Benefit from Yoga Training

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Background: It is known that children with attention deficit/hyperactivity disorder (ADHD) have deficit in executive

abilities. It is important to search for effective treatments which aim to improve executive abilities in children with this disorder. The goal of this study was to reveal effect of yoga training on executive abilities in 8-9 years of age children with ADHD. We compared the efficacy of two methods of training (yoga training vs. conventional motor exercises) in a randomized controlled pilot study.

Methods: 18 children with ADHD at the age of 8-9 years (M = 8.74 years, SD = 0.96) were included and randomly assigned to treatment conditions according to a 2×2 cross-over design. Both groups of children have participated in 12 weeks of training (body-oriented training vs. conventional motor exercises). A total of 36 training sessions lasting 30 minutes were performed. To assess the executive functions we used 3 subtests from NEPSY (Auditory Attention and Response Set, Visual Attention, Statue). Effects of training were analyzed by means of an ANOVA for repeated measurements. We have also performed qualitative neuropsychological assessment based on Luria's syndrome analysis.

Results: The ANOVA has revealed ($p \leq 0,05$) that for all subtests (Auditory Attention and Response Set, Visual Attention, Statue) the yoga training was superior to the conventional motor training, with effect sizes in the medium-to-high range (0.43-0.88). Luria's syndrome analysis has revealed in children from experimental group the improving in third functional unit of the brain which is responsible for voluntary attention and executive abilities according to Luria's approach.

Conclusions: The findings from this pilot study suggest that yoga training has positive effect on executive abilities in children with ADHD. We can propose that yoga training is one of the most effective approaches for helping children with ADHD. However, it is necessary to do further research into the impact of yoga training on children with ADHD. Particularly, we are going to reveal long-term effect of this training on executive abilities using longitudinal design.

188. Post-Stroke Deficit Prediction from Lesion and Indirect Structural and Functional Disconnection

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Behavioral deficits in stroke reflect both structural damage at the site of injury, and widespread network dysfunction caused by structural, functional, and metabolic disconnection. Two modern methods allow for the estimation of structural and functional disconnection from clinical structural imaging. This is achieved by embedding a patient's lesion into an atlas of functional and structural connections in healthy subjects, and deriving the ensemble of structural and functional connections that go through the lesion, thus *indirectly* estimating its impact on the whole brain connectome.This *indirect* assessment of network dysfunction is more readily available than *direct* measures of functional and structural connectivity obtained with functional and diffusion MRI, respectively, and it is in theory applicable to a wide variety of disorders.To validate the clinical relevance of these methods, we quantify the prediction of behavioral deficits in a prospective cohort of 132 first-time stroke patients studied at two weeks post-injury (mean age 52.8 y with range 22-77; 63 females; 64 right hemispheres). Specifically, we use multivariate ridge regression to relate deficits in multiple functional domains (left and right visual, left and right motor, language, spatial attention, spatial and verbal memory) with the pattern of lesion and indirect structural or functional disconnection. In a subgroup of patients, we also measured direct alterations of functional connectivity with resting-state functional MRI. Both lesion and indirect structural disconnection maps were predictive of behavioral impairment in all domains ($0.16<R^2<0.58$) except for verbal memory ($0.05<R^2<0.06$). Prediction from indirect functional disconnection was scarce or negligible ($0.01<R^2<0.18$) except for the right visual field deficits ($R^2=0.38$), even though multivariate maps were anatomically plausible in all domains. Prediction from direct measures of fMRI functional connectivity in a subset of patients was clearly superior to indirect functional disconnection. In conclusion, the indirect estimation of structural connectivity damage successfully predicted behavioral deficits post-stroke to a level comparable to lesion information. However, indirect estimation of functional disconnection did not predict behavioral deficits, nor was a substitute for direct functional connectivity measurements, especially for cognitive disorders.

189. Autopsy Correlations of Flortaucipir and Pittsburgh Compound B Pet in Frontotemporal Lobar Degeneration

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Objective: To examine associations between tau and beta-amyloid (Aβ) molecular PET imaging and both Alzheimer-related pathology and 4-repeat tau pathology in autopsy-confirmed frontotemporal lobar degeneration (FTLD).

Methods: Twenty-four patients had [^{18}F]-Flortaucipir PET and died with FTLD (progressive supranuclear palsy (PSP) n=10, corticobasal degeneration (CBD) n=10, FTLD-TDP type A n=3 and Pick's disease n=1). All but one had Pittsburgh Compound B (PiB) PET. Braak staging and semi-quantitative burden of Aβ plaques, neurofibrillary tangles and 4R tau pathology were performed. Flortaucipir standard uptake value ratios (SUVRs) were calculated in a temporal meta-region-of-interest (ROI) (amygdala, entorhinal, fusiform, parahippocampal, inferior temporal, and middle temporal gyri), entorhinal cortex and cortical and subcortical regions selected to match the 4R tau burden analysis. Global PiB SUVR was calculated. Autoradiography was performed in one PSP patient.

Results: Nine cases (37.5%) had diffuse Aβ plaques. Global PiB SUVR correlated with Aβ plaque burden (R_s=0.59, p=0.004) and had 100% specificity and 50% sensitivity for diffuse plaques. Twenty-one cases (87.5%) had Braak stages I-IV. Flortaucipir correlated with neurofibrillary tangle burden in entorhinal cortex (R_s=0.46, p=0.038), but entorhinal and meta-ROI SUVR were not able to detect Braak stage IV or primary age-related tauopathy (PART), at a cut-point value of positivity set at 1.27 and 1.29, respectively. Flortaucipir uptake patterns differed across FTLD pathologies and could separate PSP and CBD: flortaucipir uptake was higher in dentate nucleus of the cerebellum and red nucleus in PSP compared to CBD, and a ratio of globus pallidus to red nucleus (GP/RN) SUVR provided excellent separation of PSP and CBD (p<0.0001, area under the receiver operator characteristic curve=1.00). Flortaucipir correlated with 4R tau burden in red nucleus (R_s=0.66, p=0.004) and midbrain tegmentum (R_s=0.50, p=0.04) across patients, but not in cortical or basal ganglia regions. Autoradiography demonstrated minimal uptake of flortaucipir, although flortaucipir correlated with quantitative 4R tau burden across regions in this PSP patient, both with PHF1 (R_s=0.66, p=0.001) and with CP13 (R_s=0.68, p=0.02) immunohistochemistry.

Interpretation: Molecular PET shows expected correlations with Alzheimer-related pathology (ADNC) but lacks sensitivity to detect mild ADNC pathology in FTLD. The presence of neurofibrillary tangles with Braak stages I-IV does not seem to influence flortaucipir uptake in temporal and entorhinal cortical regions in FTLD. Regional flortaucipir uptake was able to separate CBD and PSP.

190. "Where Did the Groceries Come From?": A Case of Acute Amnestic Syndrome

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Introduction/Background: Acute amnestic syndromes (AAS) are rare clinical events where the diagnosis can be challenging with diverse underlying etiologies.[1] Transient global amnesia (TGA) is one such syndrome that is benign, self-limiting, and is characterized by sudden onset of predominantly anterograde amnesia usually lasting <24 hours without other accompanying neurological symptoms. Retrograde amnesia has also been described in some cases. Annual incidence is about 3.4 to 10.4 per 100,000, but is higher in ages >50.[1]

Objective: Early and accurate diagnosis of TGA may lead to minimizing unnecessary medical tests. Our goal is to describe a case of TGA that presented to our institution.

Case Report: 74 year-old female with a history of tobacco smoking, remote arteriovenous malformation status post proton therapy presented with symptoms of repetitive questioning and inability to register new information. Symptoms were first observed by her husband when the patient asked, "Where did these groceries come from?" The patient was unable to recall that she and her husband had gone grocery shopping the previous day. The patient continued to ask similar questions repeatedly even after being told the answers to her questions. She appeared to have understood the answers but did not register it. She was also unable to recall other events from the previous day and continually inquired about her activities from that day as well. Husband noticed she was oriented to person and place and was able to follow commands, do simple math, and name objects. Her symptoms resolved spontaneously after lasting for about 4 hours and returned to baseline memory before arrival to our emergency room. Neurological examination was normal except for recollection of events from the above episode. She had regained recollection of events from the prior day. MRI of the brain showed remote encephalomalacia in the left external capsule and the electroencephalogram was normal. Based on history, a diagnosis of TGA was made. However, a seizure as an underlying etiology for TGA is possible.

Conclusion: TGA can be a frightening experience for patients; however, it is known to be a benign syndrome with low risk of recurrence.[2] Other etiologies must also be ruled out.

References: 1. Alessandro L. J Neuro Sci. 20202. Arena JE. *Mayo Clinic Proc.* 2017

191. The Impact of Diet and Nutrients on Episodic Memory across the Adult Lifespan: A Systematic Review and Meta-Analysis

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The main purpose of this systematic review and meta-analysis is to investigate the association between diet patterns/nutrients and episodic memory across an adult lifespan. Although it has been believed that adherence to healthy diets and consumption of specific nutrients can reduce the risk of cognitive dysfunction, previous results have been inconsistent. One possible explanation for this inconsistency is the heterogeneity in domains of cognitive outcome. Therefore, this meta-analysis focused on a specific cognitive function that is significantly affected by aging: episodic memory. We aimed to estimate an effect of size of major dietary patterns (e.g., Mediterranean diet) and nutrients (e.g., vitamins, polyphenols, and omega-3) on episodic memory performance.

Eligible data have been searched from three different databases: Pubmed, Medline, and PsychoInfo. This meta-analysis utilized randomized-control trials(RCTs), longitudinal studies and cross-sectional studies. As a secondary analysis, two potential mediators, age of studied population and type of episodic memory measurements(e.g., recall vs. recognition, verbal vs. visual) are investigated. This will allow us to know if the relationship between diet/nutrition and episodic memory can be changed depending on those variables. Finally, we reviewed structural and functional brain-imaging studies that may explain the mechanism underlying the relationship between diet/nutrients and episodic memory.

192. Lizard Skin Replaces Pig Skin: Cotard's Syndrome with Zoanthropy in a Football Player Due to Presumed Chronic Traumatic Encephalopathy

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Background: Cotard's syndrome is described as the delusional belief of not only death of a body part but also includes feelings of bodily displacements and metamorphosis with replacement of a part of the body with an animal. Cotard's syndrome is seen with a variety of psychiatric illnesses including schizophrenia, bipolar disorder and depression. Furthermore, it is also associated with neurological diseases including traumatic brain injury, stroke and migraine. Chronic Traumatic Encephalopathy (CTE) in football players has been associated with a variety of neurological manifestations. Cotard's syndrome and Zoanthropy as a result of football induced presumed CTE has not heretofore been described. Such a case is presented.

Case Study: A 21-year-old right handed male, high school and college football player had multiple head injuries including loss of consciousness and helmet-to-helmet collisions on multiple occasions. Two years prior to the presentation, he became severely depressed and developed a feeling of constant movement of his neck and shoulders, with uncontrollable urge to move them, sensations of cenesthesia, that his body parts were malrotated, such that his shoulders and knees were on backwards and he couldn't recognize himself when looking into the mirror, as if it was someone else. At the same time, he observed that his hands felt, as if they were no longer his own, but rather had been replaced by a cold, reptile, lizard like hands. He claimed he was able to feel his blood flow throughout his body. He admitted having vegetative signs of depression and childhood history of migraine headaches.

Results: Abnormalities on neurological examination: Mental Status Examination: Agitated, paranoid and actively delusional. Oriented: *1. Motor examination: Dystonic posture with head hyperextended for intervals of 15-45 sec, with dystonic postures of hands hyperextended at the wrist and legs in opisthotonus like posture. Gait: Shuffling with dystonic posture in both hands. Sensory examination: Pinprick sensation decreased in right arm and hand. Other: MRI Brain: 15-20 scattered T2/FLAIR hyperintense supratentorial foci in grey-white junction.

Discussion: CTE is challenging to diagnose, by current standards. It has a pathological diagnostic criteria, but post-mortem diagnosis is too late, limiting efforts to symptom management. Those with presumed CTE should be assessed for the presence of Cotard's or other therianthropic delusions.ReferenceKudlur SNC: An overview of the neurological correlates of Cotard syndrome. Eur. J. Psychiat 2007

193. Neurogenic Maturational Correlates of the Anxiolytic Effect of Fluoxetine in Macaques

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Background: Increased adult dentate gyrus neurogenesis is suggested as a cellular mechanism underlying the anxiolytic efficacy of selective serotonin reuptake inhibitors. However, it is unclear at which stage of maturation newborn granule neurons may contribute to anxiety-related behavioral plasticity. Using a macaque model, we examined the relationship between alterations in anxiety-like behaviors and neurogenesis levels parsed by dendrite arboritic complexity following administration of fluoxetine.

Methods: Adult-born dentate gyrus neurons were detected post-mortem for 26 adult female bonnet macaques via immunohistochemistry targeting the mitotic microtubule protein doublecortin (DCX). DCX+ cells were categorized to three stages of neuronal maturation by complexity of dendritic branching: Stage 1 (primary dendrites only), Stage 2 (secondary dendrites), and Stage 3 (tertiary dendrites). Subjects had been randomized to 25 weeks of repeated separation stress or normative social housing protocols. After 15 initial weeks, subjects randomly received either a regular therapeutic dose of fluoxetine or placebo for the last 10 weeks before sacrifice (stress-fluoxetine: N=8, stress-placebo: N=7, control-fluoxetine: N=4, control-placebo: N=7). Subjects were observed three times weekly and anxiety-like behaviors were tallied to yield daily anxiety scores, averaged over three time points of interest: pre-drug, early-drug, and late-drug, corresponding to three-week blocks immediately preceding, immediately following, and seven weeks following first drug administration, respectively. Statistical associations were analyzed with general linear models. To assess behavioral changes due to fluoxetine, early-drug and late-drug mean anxiety scores were input as repeated measures and pre-drug scores as a covariate.

Results: Fluoxetine significantly boosted DCX+ counts compared to placebo at each stage of dendritic complexity, controlling for stress protocol (Stages 1-3: $p<0.01$). A significant behavioral time-point*drug-group interaction was detected ($p<0.001$). Post-hoc univariate analysis revealed that fluoxetine significantly reduced anxiety scores compared to placebo at the late-drug ($p<0.001$) but not early-drug ($p>0.3$) time point, controlling for stress protocol and pre-drug scores. Within the fluoxetine group, Stage 1 DCX+ counts predicted reductions in late-drug ($p=0.04$) but not early-drug ($p=0.18$) anxiety scores. Neither Stage 2 nor Stage 3 DCX+ counts significantly predicted behavioral changes.

Conclusions: Abundance of especially immature adult-born dentate gyrus neurons appears to most significantly

predict the anxiolytic efficacy of fluoxetine in bonnet macaques. It has been suggested that immature adult-born granule neurons enhance the inhibitory effect of mossy cells on dentate gyrus neuronal circuitry. Further investigation is needed into how this neuronal network may contribute to anxiety-related behavioral changes.

194. Fire Induced Ageusia and Anosmia

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Loss of olfactory ability in relation to fire and smoke exposure has been described in a variety of circumstances. Specifically, Chicago firefighters (Hirsch, 2000) and those who were near the World Trade Center on September 11, 2001 (Dalton, 2010) were found to have olfactory deficits. The acute effects of smoke on olfaction has also been documented in rats exposed to smoke in a laboratory (Ling, 2014) and in frequent cigarette smokers (Duffy, 2017). Anosmia and ageusia from direct exposure to extreme heat has not heretofore been described. This could be the direct result of intense heat, dust from the smoke, post-smoke or post-heat inflammatory response, or associated with the medication used to manage the post-surgical burns. Although the current patient is a frequent smoker, given the sudden dramatic drop in chemosensory ability, it is far more likely that her present inability to taste and smell was caused by the accidental fire which occurred during surgery. Further exploration of these phenomena in those who have undergone intense exposure to heat, fire, or smoke is warranted.

195. Tabescent in Amyotrophic Lateral Sclerosis: Cacogeusia without Dysgeusia

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Introduction: Cacogeusia is a dislike for the taste of food. It usually occurs concomitantly with dysgeusia, distorted sense of taste, (Hirsch, 2018). It has been associated with amylodosis (De Moor, 1994), ingestion of pine nuts (Munk, 2010) as well as H. pylori infection (Cecchini, 2013). Cacogeusia in the absence of dysgeusia, with the taste of food remaining normal, but still hedonically unpleasant, has not heretofore been described. Such a case is presented.

Methods: Case Study: A 71-year-old right-handed female presents with a six-month history of cacogeusia without dysgeusia. On presentation she complained of dry mouth that was relieved when sucking on more than 40 plus sugar free candies each day. She also noted an absence of hunger and craving for food. Four months after presentation, she complained food had negative hedonics despite possessing normal smell and taste. Liquid smoothies and cold water did not evoke such disgust nor did hot protein shakes but all solids foods were disgusting.

Results: Abnormalities in physical examination: Neurological Examination: Cranial Nerve (CN) Examination: CN IX, X: Gag absent bilaterally. CN XII: Fasciculation of tongue with percussion myotonia of the tongue. Motor examination. Bulk: atrophy in bilateral thenar and hypothenar eminences, intrinsics, pelvic girdle, shoulders, arms and feet. Spontaneous fasciculations with percussion myotonia of the tongue. Strength: intrinsics 4/5 bilateral upper extremities, 3/5 bilateral abductor policis brevis, 3/5 right gastronomies and soleus, 4/5 bilateral anterior tibialis. Chemosensation: Olfaction: Normosmia on, Alcohol Sniff Test:13, Pocket Smell Test: 3/3, Phenyl Ethyl Alcohol threshold testing: Left Nostril 6.0; right Nostril 4.5, Sucralose amyl acteate odor intensity testing and Retronasal olfactory testing: Retronasal Smell Index: 9. Gustation: normogeusia to Propylthiouracil Disc Taste Test: 10 and Taste threshold testing: Sodium Chloride, Hydrochloric Acid, Urea and Phenlythiocarbamide. EMG: fibrillation, positive wave and fasciculation in all four extremities, voluntary contraction with polyphasic unstable motor unit action potential. MRI of brain and spinal cord: hyperintense T2 flare in bilateral corticospinal tracts, left greater than right, in the brain.

Discussion: There are myriad mechanisms for the presence of cacogeusia without dysgeusia. This patient's absence of dysgeusia with perceived perception of normal taste to food suggests a cortical origin for cacogeusia. The absence of cacosmia with orthonasal olfaction but presence of cacogeusia with retronasal olfaction implies that the primary abnormality is not due to end organ dysfunction to the olfactory system. Further investigation is warranted.

196. An Unusual Case of Stalking: The Neurologic Implications of Erotomania in Decompensated Schizoprenia

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Background: The accurate definition of stalking may differ through different legal or cultural contexts, however it is generally defined as persistent intrusive monitoring of an individual. Individuals that exhibit stalking behaviors commonly have some type of delusional disorder, frequently Erotomanic type. However, most research suggests that successful stalking would require the perpetrator to have experience, careful planning, actions which would require higher cortical functioning which often is not observed in schizophrenic patients. Schizophrenia is a psychiatric illness where the patients have gross decline in global functioning. Neurological changes in schizophrenics often render them to a disabled state where they cannot have normal daily functioning that necessitate meticulous use of executive functions. Here we present a patient with Schizophrenia and a history of medication noncompliance, now in a decompensated state presenting with erotomania. The patient has maintained this delusion and acted on it by stalking an individual in an elaborate and planned fashion which brought major concern to the individual being stalked before the patient was ultimately involuntarily hospitalized.

Methods: A literature review was conducted using PubMed, NCBI, and ScienceDirect using the following keywords: Cognitive execute function and Schizophrenia, stalking and Schizophrenia, frontotemporal deficits and stalking, frontotemporal deficits and erotomania, global dysfunction brain schizophrenia, stalking, typology of stalking,

stalking and mental illness, stalking and mental disorders, meta-analysis stalking mental illness. This yielded 16 publications to analyze stalking behavior, erotomania, and patients who are likely to exhibit such behavior. However, in this case no papers were found of decompensated schizophrenics exhibiting erotomania which directly resulted in stalking or criminal behavior. We also seek to demonstrate the difficulty in treating such patients in an inpatient setting and the challenges of creating effective discharge plans.

Results: Patient was stabilized on new regimen of antipsychotic and mood stabilizer. He developed insight into his behaviors and illness. Patient consented to long acting injection medication and regular follow ups. Patient was also placed in new residential housing to minimize interaction with the victims.

Conclusion: This case illustrates that even in a decompensated state, Schizophrenic patients may be able to successfully execute the higher cognitive and executive function required for complex stalking behavior. This case presents difficulty in patients with such capabilities as they can relapse into their obsessive stalking behavior once their stimulus is reintroduced to them in an uncontrolled setting.

197. Dissociable Systems for Recognizing Places and Navigating Through Them: Causal and Developmental Evidence

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Humans recognize a place or "scene" in a fraction of a second and almost simultaneously navigate that scene flawlessly and effortlessly. Recent functional MRI (fMRI) evidence suggests that human visual scene processing is supported by at least two functionally distinct systems; one for visually-guided navigation, including the occipital place area (OPA), and one for scene categorization (i.e. recognizing a city vs. a beach), including the parahippocampal place area (PPA). It is unknown, however, whether these systems arise along differential timelines in typical development and whether they are causally dissociable - possibilities that would greatly strengthen the claim that these systems are in fact distinct. Here we addressed these questions by testing navigation and categorization abilities in typically developing children ages 4 to 8, as well as adults with Williams syndrome (WS), a genetic disorder involving cortical thinning in and around the OPA. During the categorization task, participants imagined standing in a room, and indicated whether they were in a bedroom, kitchen, or living room. During the navigation task, participants imagined walking through the room and indicated whether they could leave through a door on the left, center, or right wall by following a path on the floor that only connects to one of the three doors. We found that i) navigation and categorization develop along differential timelines in typical development, with the navigation maturing more slowly across childhood than the categorization system; and ii) that WS adults are selectively impaired in navigation relative to mental-age matched controls (i.e., typical developing 7 year olds). Taken together, our results provide the first developmental and causal evidence for dissociable visually-guided navigation and scene categorization systems, and further suggest that this distinction may have a genetic basis.

198. Haptic Training Enhances Visual Executive Attention

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The idea that pure haptic training improves executive attention is appealing and has clinical significance. However, the neural mechanism of this training effect remains largely unknown. Using high-density electroencephalography (EEG), we found that participants with pure haptic training outperformed nontrainees in the executive control network in the Attention Network Test (ANT). We also found that this phenomenon was associated with N200 and P300 effects, namely,N200 amplitude reductions, P300 latency reductions and P300 amplitude enhancements. In addition, stronger activation was demonstratedamongthe trainees in sensorimotor regions at N200 and in prefrontal regions at P300. In addition, pure haptic training was found to enhance the functional connectivity between frontal-parietal exchanges in beta frequency at P300. Our results suggest that improved executive attention through pure haptic training may rely on hierarchical processing, including stronger functional connectivity of the frontoparietal network and finer representation in the sensorimotor and prefrontal cortices, which are regions involved in top-down sensorimotor integration and conflict resolution. These findings may help illustrate the potential use of haptic training in attention enhancement across sensory channels and cognitive impairment amelioration.

199. Enhancing Frontal Dopamine Tone Improves Working Memory Maintenance

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The contents of working memory must be maintained in the face of distraction, but updated when appropriate. To manage these competing demands of stability and flexibility, maintained representations in working memory are complemented by distinct gating mechanisms that selectively transmit information into and out of memory stores. The operations of such dopamine-dependent gating systems in the midbrain and striatum, and their complementary dopamine-dependent memory maintenance operations in cortex, may therefore be dissociable. If true, selective increases in cortical dopamine tone should preferentially enhance maintenance over gating mechanisms. To test this hypothesis, tolcapone, a catechol-O-methyltransferase

inhibitor that preferentially increases cortical dopamine tone, was administered in randomized, double-blind, placebo-controlled, within-subject fashion to 49 healthy subjects who completed a hierarchical working memory task that varied maintenance and gating demands. Tolcapone improved performance in a condition with higher maintenance requirements and reduced gating demands, reflected in a reduction in the slope of response times across the RT distribution. Resting state fMRI data demonstrated that the degree to which tolcapone improved performance in individual subjects correlated with increased connectivity between a region important for first-order stimulus-response mappings (left dorsal premotor cortex) and cortical areas implicated in visual working memory, including the bilateral intraparietal sulcus and left fusiform gyrus. Together these results provide evidence that augmenting cortical dopamine tone preferentially improves working memory maintenance.

200. Effects of Viral Load on Neuroimaging and Neuropsychological Performance in HIV-Positive Adults

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Studies examining the effects of viral load (VL) on brain integrity in human immunodeficiency disorder (HIV) often combine people on and not on combination antiretroviral therapy (cART), and use differing cutoffs for defining virologic control. We used classifications recommended by the Department of Health and Human Services to compare HIV- individuals and people living with HIV (PLWH) on stable cART at differing levels of virologic control on measures of cognition and brain volumes, both cross-sectionally and longitudinally. 349 PLWH on stable combination antiretroviral therapy (cART) with differing degrees of virologic control ("virologic suppression" (VL ≤ 20 copies/mL), "low-level viremia" (20 copies/mL < VL ≤ 200) or "virologic failure" (VL > 200 copies/mL)), and 195 HIV- controls were recruited. Participants completed a comprehensive neuropsychological battery and a magnetic resonance imaging (MRI) scan. The three PLWH VL groups and the HIV- control group were compared on five cognitive domains (learning, retention, executive functioning, motor/psychomotor, language), a global cognition score, cortical brain volume (total cortical volume; frontal, parietal, temporal and occipital lobes), and subcortical brain volume (total subcortical volume; thalamus, caudate, putamen, pallidum, hippocampus, amygdala). Correlations examined relationships between cognition and brain volumes. Longitudinal analyses (average length between visits = 23.9 months) compared change in cognition and brain volumes between PLWH who were VS at both visits (n=80) or VF at both visits (n=18). Significant omnibus group differences (p<.01) were observed across cognition (learning, executive function, motor/psychomotor, language, global) and brain volumes (total cortical and subcortical, frontal, parietal, temporal, thalamus, caudate, putamen, hippocampus, amygdala). Pairwise comparisons identified significant differences primarily between the HIV-control and virologic failure group, with few differences between the PLWH who had virologic suppression or low-level viremia. Executive function and motor/psychomotor performance correlated with total cortical and total subcortical volume, respectively (p<.05). Longitudinally, PLWH who were classified as VF at both study visits had an increased rate of decline in total subcortical volume (p<.001) and motor/psychomotor speed (p=.017) compared to PLWH who were classified as VS at both visits. Results indicated a lack of a significant VL association with brain integrity in PLWH until VF. VF over a longitudinal period was associated with a greater decline in brain integrity. Other factors, such as initiating cART soon after diagnosis or management of comorbidities may have a larger impact on disease outcomes as long as VL remains <200 copies/mL.

201. SSRIs May Mitigate the Relationships between Depression and Language Output and between Depression and Lesion Volume after Stroke

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Stroke is the leading cause of adult disability worldwide and results in depression in about 30% of patients. Post-stroke depression is often treated with selective serotonin reuptake inhibitors (SSRIs) which may also influence motor and cognitive recovery (but not overall recovery measured with the Modified Rankin Scale). We hypothesized that language content would negatively correlate with depression, and both would correlate with lesion volume, but that these relationships might be mitigated by SSRI use.

Methods: We enrolled 54 patients with acute ischemic stroke (mean age=61.2±13.5 years, mean education=14.6 years, 46% female) in a study of language recovery and its relationship with lesion volume, depression, and SSRI use. 19 patients were prescribed an SSRI for at least 90 days post-stroke onset, and 35 were not prescribed SSRIs (controls). Language and depression measures were gathered at acute (3±2 days post-stroke) and chronic (6 months±2.8 years post-stroke) time points. Language abilities were measured using content unit (CU) scores from the Boston Diagnostic Aphasia Examination Cookie Theft picture description task, which assesses content of narrative speech. Depression was assessed using the Patient Health Questionnaire-9 (PHQ9) brief depression index. Lesion volumes were traced manually on acute clinical Diffusion Weighted Images and volumes were extracted using NiiStat software. Pearson correlations were calculated between variables.

Results: CU negatively correlated with lesion volume at baseline in the SSRI group (r=-0.57; p=0.014) and controls (r=-0.48; p=0.0041) and negatively correlated with depression score only in controls (r=-0.60; p=0.038). Patients without SSRIs produced less content in proportion the degree of depression. Greater improvement in CU was associated with lower baseline CU in both groups (r=-0.50; p=0.029; r=-0.35; p=0.040). Depression severity correlated with lesion volume in controls at acute (r=0.84; p=0.0011) and follow-

up (r=0.60; p=0.025) time points. For the SSRI group, lesion volume did not correlate with depression severity at either time point. Of note, acute lesion volume did not differ significantly between the two groups (W=281; p=0.533).

Discussion: These results suggest that SSRI use for at least 3 months post-stroke might mitigate the correlation between depression severity and narrative speech content and between depression severity and acute lesion volume at both acute and chronic time points. Larger studies are needed for multivariable analyses to determine the independent predictors of depression and narrative speech output. Findings could have implications for language function and recovery.

202. Weakness of Memory in Delayed Recall Condition is Specific Deficit in Children with ADHD

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Background: It is known that children with ADHD have deficit in executive abilities, particularly they have weakness in working memory [Barkley, 1997]. However, it is important to identify the specificity of deficit in executive abilities for children with this disorder. Do children with ADHD have global or specific deficit in memory? The goal of this research was to examine the hypothesis that preschool children with ADHD have specific deficit in memory in delayed recall condition in comparison to immediate condition.

Methods: The experimental group consisted of 18 children with ADHD at the age of 5-6 years (M = 5.47 years, SD = 0.95, 15 boys and 3 girls). The control group included 18 typically developing (TD) children. TD children were free of medical, cognitive, language, sensory, and motor impairments according to their medical certificates. Children from experimental and control groups were matched for IQ, gender and age. Children from both groups were assessed with verbal memory subtest from child neuropsychological battery. This subtest is designed to assess the reproducing 7 words in immediate and delayed recall conditions. Children were asked to repeat words immediately and 10 minutes after learning. Children had one attempt for both conditions. Children performed the physical exercises between two stages of memory subtest. ANOVA with repeated measures was used to reveal group differences in reproducing the words in two conditions.

Results: We have not revealed significant (p≤0,05) differences between children from experimental and control group in reproducing the words in immediate recall condition. However, the interaction of condition type and group was significant [F(1,34)=8,12; p=0,003)]. Children with ADHD had worse results in reproducing the words in delayed recall condition in comparison to children from control group.

Conclusions: This research shows that preschool children with ADHD have weakness in verbal memory in delayed recall condition. It can be proposed that preschool children with ADHD have specific (not global) deficit in memory for delayed recall condition. We assume that deficit for memory in delayed recall condition can be one of the key symptoms in attention deficit/hyperactivity disorder. However, we need to do further research to prove this hypothesis. Particularly, we plan to do longitudinal investigation of children with ADHD for revealing this deficit in school-age period.

203. A Case of Hallucinations and Palatal Myoclonus: Unraveling the Truth

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Objective: To report an unusual case of visual, tactile, and auditory hallucinations with dementia, essential tremors, and palatal myoclonus.

Background: Palatal myoclonus is usually associated with hypertrophic olivary degeneration and caused by lesions in the triangle of Guillain and Mollaret. It can be seen secondary to various disorders including stroke, demyelination, infections, trauma, and neurodegeneration. Hallucinations can also be seen in brain stem lesions including mid-brain.

Design/Methods: N/A

Results: Here, we report the case of an 82-year-old man with the past medical history of an alcohol use disorder, coronary artery disease, macular degeneration, transient ischemic attack, idiopathic hypertrophic olivary degeneration and cerebellar degeneration presenting with hallucinations, cognitive decline and palatal myoclonus that began one year ago following head trauma. This was followed by episodes of vivid visual, tactile and auditory hallucinations that have gradually progressed. The patient was also found to have palatal myoclonus and mild intention tremors. The initial exam was notable for poor memory and fluency, chronic vision loss and palatal myoclonus. Motor examination revealed normal muscle strength and bulk with mild intention tremor without parkinsonian symptoms. Sensory examination was notable for positive glabellar reflex, proprioceptive impairment, and unsteady gait with a short pace. Reflexes were normal throughout with no clonus. Laboratory examination was unremarkable; MRI of the brain was suggestive of hypertrophic degeneration of the inferior olivary nucleus. No gross lesions were seen in the Guillain Mollaret triangle; in addition, there was confluent white matter signal abnormality suggesting severe microvascular deep white matter ischemic disease. PET brain showed regions of hypermetabolism in the right anterolateral temporal cortex and cerebellum just posterior to the dilated 4th ventricle. The patient was placed on Seroquel with some improvement in hallucinations but was later discontinued due to intolerable side effects.

Conclusion: Our case demonstrates a myriad of symptoms, including hallucinations with dementia, tremors, and palatal myoclonus, with image findings that cannot be explained by one unifying diagnosis. The association of hallucinations with the patient's other symptoms and vascular changes is unclear. This presents the question of whether such anatomical changes, as seen in this patient, lead to hallucinations, or are these parts of the spectrum of a new disease process.

204. Eye Movements Abnormalities as Early Biomarker of Alzheimer's Disease: An Ecological Approach

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Background: Alzheimer's disease (AD) is the most common type of dementia. Often AD patients are diagnosed after the onset of cognitive symptoms, when the neurodegenerative process has already reached an advanced stage. Thus, the challenge around the world has been to find early and easy biomarkers of degeneration. Interestingly, brainstem structures, including the Superior Colliculus (SC), a structure involved in eye fixation and saccadic eye movements (Munoz, *Can. J. Physiol. Pharmacol.,* 2000), shows neurofibrillary changes earlier than cortical areas (e.g., Uematsu, *Acta Neuropathol Com*, 2018). Moreover, the SC shows an intrinsic vulnerability to tau pathology (Armstrong, *Optom Vis Sci*, 2017) and neuronal loss in AD patients (Erskine, *Am J Geriatr Psychiatry*, 2017). We hypothesized that AD-related eye movement abnormalities that are commonly observed in laboratory tasks (Anderson, *Nat. Rev.,* 2013) could be potentially detected during free-viewing and Mild Cognitive Impairment (MCI).

Methods: N=29 AD (14F, M_{age}=75.9), 29 MCI (11F, M_{age}=72.1) patients, and 18 age-matched healthy controls (HC; 10F, M_{age}=71.7 years) were recruited at the Memory center of Clinica Neurologica of the Padova University Hospital (Italy). Participants' cognitive status was assessed with the Montreal Cognitive Assessment (MoCA). They were also asked to freely explore a series of 20 real-world images presented on a computer screen while recording eye movements (sampling-rate: 1000Hz). A set of standard eye movements metrics was computed (e.g. fixation duration, saccade amplitude, etc). In addition, we computed a novel metric on the number of fixations out of the image area, a measure of weakened saccade inhibition, and two measures of gaze spatial variability and cognitive control, respectively (the Stationary Gaze Entropy, SGE, and the Gaze Transition Entropy, GTE; see Shiferaw, *Neurosci Biobehav R,* 2019).

Results: AD patients showed lower mean saccade amplitude (p=.035) and a less variable pattern of fixation duration (i.e., SD; p=.037) as compared to HC. The number of out-of-image fixations reflecting a loss of inhibition negatively correlated with the MoCA score in AD (r=-.37, p=.047) and MCI (r=-.46, p=.49). There was also a negative correlation between SGE and GTE in AD (r= -.41; p=.031) indicating that higher variability correlated with weaker cognitive gaze control (Shiferaw, *Neurosci Biobehav R,* 2019).

Conclusion: Spontaneous eye movement behavior in free viewing can reveal subtle alterations in MCI and AD patients. Further research is necessary to strengthen our observations and link them to other biological and imaging biomarkers.

205. Guideline for Repetitive Transcranial Magnetic Stimulation Treatment of Major Depressive Disorder Using Resting State Functional Magnetic Resonance Imaging

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Introduction: Subjects diagnosed with major depressive disorder (MDD) have shown reduced frontal activation in default mode network (DMN) and fronto-parietal control network (FPC) in the analysis of resting state functional magnetic resonance imaging (rs-fMRI). In addition, the integrity and bilateral homogeneity of the FPC were also evaluated, and -taking into account the activation and subsequent normalization regard to DMN- low oxygenation consumption regions were defined in the attention network. MDD is considered the main clinical application of repetitive transcranial magnetic stimulation (rTMS) and recent studies highlighted the need to improve the spatial guidance of this therapy to improve its efficiency and the therapeutic evaluation of patients.

Methodology: rs-fMRI were acquired pre and post rTMS application, in twelve patients diagnosed with MDD (according to DSM-V criteria). A complete psychiatric, neurological, psychological and neuropsychological assessment was carried out, including anxiety scales, mood scales and sleep inventory (HARS, STAI, HADRS, MADRS, PSQI). The neuropsychological assessment: Stroop Test, Matrix Reasoning, Toulouse Test, RAVLT, RCF, Digit Span and F.A.S. A follow-up control was performed six months later with the Clinical Global Scale (CGS). The rTMS protocol consisted of 30 sessions of high frequency l-DLPFC rTMS (5 sessions per week). A total of 1400 pulses were applied at 110% of the motor threshold, guided by the eloquent areas found with the pre rs-fMRI study processed with FSL (Oxford) and CONN (MATLAB) software. The independent component analysis (ICA) technique was implemented to define and quantify the signal generated by the DMN and FPCs networks.

Results: The scores obtained on both clinical scales and neuropsychological tests improve. These results are consistent with a better quality of life reported. The rs-fMRI post-treatment analysis showed homogenization of the FPCs networks and a better signal standardization respect to those found with the DMN.

Discussion: Normalizing the signal of the FPCs networks from the DMN network, is a method that allows to guide and standardize the lateralization and location of the application area in rTMS therapy. Intermittent networks identified with ICA methodology could be more related to assessing and monitoring MDD, however, this practice would require better sensitivity in the rs-fMRI protocol. Seed methods could improve the location of the area involved in MDD, which will require more advanced post-processing methods than those implemented in this study.

206. Lesion Network Mapping of Mania Symptoms Caused by Focal Brain Lesions

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Background: While mania is characteristic of Bipolar I Disorder, it has been reported following focal brain lesions for nearly a century. The localization of secondary manic symptoms is poorly understood, as mania has been reported following damage to multiple brain locations.

Objective: We utilize the human connectome to study cases of mania following focal brain lesions, provide insight into brain regions responsible for manic symptoms, and identify potential therapeutic targets.

Methods: We identified two independent patient cohorts with mania attributed to focal brain lesions; a literature cohort from published case-reports (n=41) and a clinical cohort from chart review (n=15). Lesion locations were mapped onto a common brain atlas. The network of brain regions functionally connected to each lesion location was computed using normative human connectome data (resting-state fMRI, n=1000). Results were compared to lesion locations not associated with mania (n=569), lesion locations associated with symptoms potentially related to mania (n=274), and transcranial magnetic stimulation sites reported to induce/relieve mania symptoms.

Results: Lesion locations associated with mania were heterogeneous; no single brain region was lesioned in all or even most cases. However, these lesion locations showed a unique pattern of connectivity to the right-sided orbitofrontal cortex, right inferior temporal gyrus and right frontal pole. This connectivity profile was reproducible across independent cohorts, matched that of lesions associated with co-morbid symptoms, and aligned with effects of therapeutic brain stimulation on mania symptoms.

Conclusions: Brain lesions associated with mania are characterized by a specific pattern of brain connectivity that appears relevant for understanding co-morbid symptoms and identifying therapeutic targets.

207. Unveiling the Presence and Nature of Auditory Comprehension Deficits in Primary Progressive Aphasia

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Objectives: We hypothesized that: 1. word/picture verification would be a more sensitive measure of single-word auditory comprehension impairment than a word/picture matching task in PPA, and 2. semantic errors would be the predominant error type on word/picture verification in logopenic variant PPA (lvPPA) and semantic variant PPA (svPPA), but not in nonfluent agrammatic PPA (nfaPPA) because single-word comprehension and semantic knowledge are spared in nfaPPA and remain relatively intact over time.

Design/Methods: Seventy individuals with PPA (mean age = 69.56 + 7.96 years; mean education = 16.23 + 2.56 years; mean symptom duration = 45.01 + 22.45 months; 53% female) completed Semantic Word Picture Matching (SWPM) (Rogalsky et al., Neurocase, 2011) and a noun and verb word/picture verification task (Newhart et al., Cognitive and Behavioral Neurology, 2007; Rapp & Caramazza, Journal of Neurolinguistics, 2002).

Results: Forty-two individuals (60%) performed normally (> 90% correct) on both tasks. Of the 28 who demonstrated impaired performance (< 90% correct) on at least one task, 19 (27%) demonstrated impaired performance on word/picture verification, but unimpaired performance on word/picture matching. Of these 19 individuals, 12 (63%) were lvPPA, 3 (16%) were nfaPPA, and 4 (21%) were svPPA. More than one-third of those with lvPPA (12/34, 35%) and svPPA (4/11, 36%) were diagnosed as impaired on word/picture verification, but unimpaired on word/picture matching. The word/picture matching task identified 9 (13%) individuals as impaired whereas the word/picture verification task identified 61 (87%) individuals as impaired (Fisher Exact Test = 0.0001, $p<0.05$). Errors on word/picture verification were due to semantic rather than phonologic foils in lvPPA ($p=0.02$) and svPPA ($p=0.01$), but not in nfaPPA.

Conclusion: Word/picture verification was a more sensitive measure of single-word auditory comprehension deficits in PPA than word/picture matching, unveiling impairment in over one-third of those with lvPPA and svPPA identified as unimpaired on word/picture matching. This finding is consistent with our prior work that degradation of auditory comprehension/semantic knowledge may be under-recognized in lvPPA. Single-word auditory comprehension deficits were due to semantic rather than phonologic errors in lvPPA and svPPA, but not in nfaPPA. This finding suggests that distributed models of semantic access can be applied in language impairment in neurodegenerative disease and can help in distinguishing lvPPA from nfaPPA.

K-595. Fetal Brain Development In Congenital Heart Disease

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Background: Congenital heart disease (CHD) is associated with neurodevelopmental disability and abnormal brain development *in utero*. We applied advanced fetal neuroimaging techniques to determine whether reduced cerebral substrate delivery impacts the brain globally, or in a region-specific pattern that may suggest neuroprotective targets. We also explored the separate contributions of cerebral substrate delivery andgenetic/environmental factors to fetal brain development.

Methods: We enrolled 179 pregnant women in a prospective, longitudinal fetal MRI study from 2014-2018 comprised of four groups of fetuses: "HLHS/TGA," with either hypoplastic left heart syndrome (HLHS) or transposition of the great arteries (TGA), diagnoses that carry especially high risk of diminished fetal cerebral substrate delivery; "CHD-Other," with other CHD diagnoses; "CHD-Related Control," healthy with a family history of CHD; and "Optimal Control," healthy without a family history of CHD. We excluded fetuses with extracardiac anomaly or genetic syndrome. MRI and echocardiogram/Doppler were obtained at 18-30 and 36-40 weeks gestation. Random effect regression models were used to assess group differences in brain volumes and relationships to hemodynamic variables.

Results: The HLHS/TGA (n=24), CHD-Other (50), and CHD-Related Control (34) groups had generally smaller brain volumes than the Optimal Controls (71). Compared with the CHD-Related Controls, the HLHS/TGA group had smaller subplate zone (-13.7% [standard error=4.3%], P<0.01) and intermediate zone (-13.9% [4.3%], P<0.01) volumes on early MRI. These findings persisted in a longitudinal analysis of aggregate subplate/intermediate zone (-7.6% [1.7%], P<0.05). The ventricular zone showed a comparable volumetric reduction (-7.3% [1.9%], P=0.07). Smaller volumes of these vulnerable brain regions were independently associated with single ventricle status, worse calculated substrate delivery score, and lower cardiac output (each P<0.05).

Conclusions: CHD is associated with smaller fetal brain size beginning before 30 weeks gestation and varying across brain regions. Brains of fetuses with CHD were more similar to fetuses with a family history of CHD than to those of an optimal comparison group. CHD may be associated with a genetic and/or environmental background of developmental brain differences with superimposed effects of oxygen and/or nutrient deficiency on selectively vulnerable fetal brain structures.

Cerebrovascular Disease

256. Is Motor Recovery after Ischemic Stroke Proportional? Consideration on Ceiling Effect of Fugl-Meyer Assessment Scale

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Objective: This study aimed to check the validity of the proportional recovery model for motor recovery of upper extremities after ischemic stroke.

Methods: We reviewed the medical records of patients who were enrolled between August 2012 and May 2015 in the Korean Stroke Cohort for Functioning and Rehabilitation. We excluded patients with hemorrhagic stroke, cerebellar lesions or lesions in the bilateral hemispheres, a history of surgery including craniectomy, progression of ischemic lesion, hemorrhagic transformation, stroke recurrence or any neurological deterioration up to 6 months after stroke, missing values in the Fugl-Meyer Assessment upper extremity subscore (FMAUE) at 1 week or 6 months post stroke or history of post stroke complication. Recovery proportion was defined as the actual change in FMAUE between 1 week and 6 months post stroke over the initial neurological impairment, '66 - initial FMAUE'. We collected clinical variables such as age, sex, characteristics of the ischemic lesions, etiology and location of ischemic lesions, and type of intervention. We used propensity score matching and logistic regression to verify that recovery proportion is fixed to 0.7. To confirm that there is no valid linear regression model predicting change of FMAUE between post stroke 7 days and 6 months, we checked normality of residuals. We also analyzed covariance and correlation between initial neurological impairment and change of FMA to postulate a novel model for motor recovery of upper extremity after stroke.

Results: We screened 10,636 patients and analyzed 734 patients (mean age, 65.5 $\pm$ 12.1; female, 275 [37.5%]) with first-ever ischemic stroke. Mean recovery proportion was 0.74 $\pm$ 0.39. We demonstrated that initial neurological impairment affect the recovery proportion through propensity score matching. We also confirmed that initial neurological impairment affect the probability of reaching full neurological recovery, which means follow-up FMAUE 66, through logistic regression analysis. We showed that any multivariate linear regression model predicting change of FMAUE does not satisfy the normality of residuals, whether considering the ceiling effect of FMAUE or not.

Conclusion: We demonstrated that the data of this study is in accordance with that of previous studies, which showed the ceiling effect of Fugl-Meyer Assessment score. Our results showed that initial neurological impairment affects the recovery proportion. We postulated a novel model for motor recovery of upper extremity which determines recovery proportion according to initial neurological impairment.

257. Decline in Stroke Alerts and Hospitalizations During the COVID-19 Pandemic

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Introduction: Patients with stroke-like symptoms may be underutilizing emergency medical services and avoiding hospitalization during the coronavirus infectious disease 2019 (COVID-19) pandemic. We investigated a decline in emergency department (ED) stroke alert activations and admissions for stroke and transient ischemic attack (TIA).

Methods: We retrospectively compiled total weekly ED stroke alerts and hospital admissions between 12/31/2018 and 4/7/2019 versus 12/30/2019 and 4/5/2020 at five U.S. tertiary academic comprehensive stroke centers in cities with early COVID-19 outbreaks in Boston, New York City, Providence, and Seattle. We collected data on admission stroke severity using the National Institutes of Health Stroke Scale (NIHSS). Time series regression models (autoregressive integrated moving average: ARIMA) and time series forecasting systems were used to assess the interrelationship of weekly stroke alerts and admissions, separately. The standard variation of weekly stroke alerts and admissions were compared to the same measures in 2019.

Results: Compared to 12/31/2018-4/7/2019, a decline in stroke alerts and admissions occurred during 12/30/2019-4/5/2020 ($p<0.001$ for each). The declines coincided with state stay-at-home recommendations in late March. The greatest decline in cases was observed between March 23 and April 5, 2020, where 156 admissions represented a 39% decline compared to the corresponding weeks in 2019. At three centers with 2019/2020 stroke alert data there was a 25% decline in alerts compared to 2019. The median NIHSS for all centers was 10 and 11 for the weeks of March 23 and 30, 2020, versus a median NIHSS of 7 and 11 for the weeks of March 25 and April 1, 2019.

Conclusion: At these five large academic U.S. hospitals, ED stroke alerts and admissions for stroke and TIA declined during the COVID-19 pandemic. Acute stroke therapies are time-sensitive, so decreased healthcare access or utilization may lead to more disabling or fatal strokes, or more severe non-neurologic complications related to stroke. Our findings underscore the indirect effects of this pandemic. Public health officials, hospital systems, and healthcare providers must continue to encourage stroke patients to seek acute care during this crisis.

258. Polypill Trials for Stroke Prevention — Main Results, Critical Appraisal, and Implications for US Population

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Objective: summarize the main results of the polypill trials relevant to stroke prevention, and their potential applicability to the US population.

Background: Stroke is a leading cause of morbidity and mortality in Americans. The polypill, referring to a variety of combinations of low-cost cardiovascular and stroke preventive medications combined in a single tablet, has been evaluated as a population-based approach for cardiovascular disease prevention in several trials. An estimated 50% reduction in the 5-year stroke incidence can be achieved with this strategy. This review summarizes the scope of the problem, main trial results, and their potential applicability to the US population.

Design/Methods: An in-depth review and critical appraisal of the polypill clinical trials relevant to stroke prevention.

Results: Initial trials demonstrated the efficacy of the polypill approach. Trial designs differed in the number of study participants, inclusion criteria, the choice of comparator groups, polypill components and their dosages, and the duration of the observation period. The most recent, the PolyIran study, showed the effectiveness of one form of a polypill for cardiovascular disease prevention, high medication adherence, and low adverse event rates.

Conclusions: Although health care providers should continue to encourage patients to adhere to traditional cardiovascular disease prevention strategies, a population treatment approach based on wide scale use of a polypill has emerged. None of published polypill trials focused on stroke as the primary outcome and most were conducted in developing countries, limiting generalization to the US population. A US-based randomized trial with stroke as the primary outcome is needed to assess the usefulness of this approach for stroke prevention in the United States.

259. Retrospect Diagnosis of Hypoxic-Ischemic Cortical Blindness in a Patient Manifesting with Presumed Nonorganic Vision Loss — Case Presentation and Lessons Learned

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Objective: Distinguish organic from nonorganic vision loss by using maneuvers to demonstrate the presence or absence of intact vision.

Background: Nonorganic vision loss (NVL), albeit common, is often challenging to diagnose and can sometimes coexist with organic disease. Cortical blindness has been associated with hypoxic-ischemic (HI) injuries and the occipital lobe can be an isolated target.

Design/Methods: We report disabling organic vision loss in a young patient manifesting with assumed NVL, and further investigations revealed HI brain injury.

Results: A young lady presented with acute painless binocular visual loss and pleuritic chest pain in the setting of reported domestic abuse incident addressed by police officers. Notable recent recovery from a hospitalization for status asthmaticus that required few days of intubation. Patient had history of ADHD treated with amphetamine, anxiety, polysubstance abuse undergoing maintenance treatment with Suboxone®, and recent cocaine use. Initial ophthalmologic examination was unremarkable, except for light perception OU. The patient was provisionally diagnosed with NVL. Repeat examination by neurology was notable for signs suggestive of organic vision loss such as absent optokinetic nystagmus. We have failed to demonstrate the presence of intact vision by using other relevant maneuvers. Further investigations pursued. Laboratory data revealed bilateral

subsegmental pulmonary embolism and anticoagulation therapy was started. Repeat MR brain scans revealed evolved sequela of global HI event with subacute cortical ischemia in bilateral occipital lobes. No evidence of dural venous sinus or cortical vein thrombosis. Lumbar puncture and CSF analysis was unremarkable. Extensive infectious, rheumatologic, hematologic, immunologic, and oncologic evaluation was unremarkable for a specific etiology.

Conclusions: NVL is a diagnosis of exclusion. The main goal of evaluation is to eliminate an organic disorder. If any signs of organic disease are detected, further investigations should be pursued as appropriate.

260. Adapting a Stroke Preparedness Music Video for a High Stroke Risk Population

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Background: Treatments for stroke reduce disability, but are time sensitive. Innovative stroke preparedness interventions, focusing on stroke symptoms and the importance of calling 911, are needed. The objective of the current research was to adapt a video stroke preparedness intervention for patients attending community health centers (CHCs), a population at high risk for stroke, using a community based participatory research approach.

Methods: In partnership with a Flint, Michigan CHC network, we conducted semi-structured interviews with community health workers (CHWs) and CHC patients. We showed the CHWs a 3.5-minute stroke preparedness music video previously created for African American church members. We interviewed CHWs about implementation of the video and its acceptability for their patients. We then conducted semi-structured interviews of CHC patients to determine the video understandability, acceptability, cultural appropriateness, and to explore opportunities for improvement. Interviews were recorded and transcribed verbatim. Coding was then performed according to grounded theory methodology by identifying the common themes in the interview responses.

Results: 2 out of 3 CHWs were interviewed. One CHW could not be reached for interview despite multiple attempts. The CHWs were satisfied with the video. Suggestions for improvement included adding a personal story from a stroke patient and a spoken statement, in addition to the music lyrics, about the importance of calling 911. Both CHWs thought the video could be shown at the end of a patient visit. Both CHWs thought that lack of internet access might be a barrier to showing the video at a home visit, but provided solutions such as carrying a smart phone or iPad on which the video was saved. We interviewed 25 CHC patients with a mean age of 45 $\pm$ 3 years old, 72% African American, and 52% female. Most participants found the video acceptable and understood that the main message of the video was to recognize signs of a stroke and call 911. Participants liked the gospel tune and thought the length was appropriate. Suggestions for improvement included adding more role play/discussion of stroke signs.

Conclusions: Tailoring of interventions may be most effective when the end-users, in this case CHWs and patients, contribute to the design and adaptation process. CHC patients will be co-creators of the intervention as the video will be modified based on their feedback. Collaborating with CHWs resulted in strategies for future implementation of the video.

261. FLAIR Hyperintense Vessel Rating to Predict Penumbra in Acute Stroke

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The NIHSS is a standard tool for measuring severity of acute stroke. Because it is heavily weighted on motor dysfunction, it often does not capture deficits associated with cortical penumbra dysfunction, particularly in right hemisphere (RH) stroke. Tests of neglect have correlated more strongly than NIHSS score with volume of tissue dysfunction (infarct + penumbra) in RH stroke. Penumbra is typically identified with CT perfusion or MRI perfusion-weighted imaging (PWI). However, perfusion imaging is not universally available or possible due to contrast contraindications. Fluid Attenuated Inversion Recovery (FLAIR) sequences, however, are typically obtained in clinical MRI without contrast. In hypoperfused regions, loss of flow voids causes arteries supplying the territory to appear bright on FLAIR; the number of FLAIR Hyperintense Vessels (FHV) correlates with and can be used to estimate volume of hypoperfusion measured with PWI. We used FHV scoring to estimate volume of penumbra, and to determine the correlation with NIHSS scores in acute RH and left hemisphere (LH) stroke. We studied 157 adults (71 LH) within 48 hours of acute stroke. Mean NIHSS was 4.3 ($\pm$4.16). Six vascular areas were evaluated: ACA territory, PCA territory, MCA territory-frontal lobe, MCA-temporal, MCA-parietal, and MCA-insular. Penumbra in cubic centimeters was estimated by hypoperfusion volume (FHV x 16) minus infarct volume when hypoperfusion volume exceeded infarct. Total dysfunctional tissue was estimated by infarct volume + penumbra. In LH stroke, NIHSS score correlated more strongly with volume of tissue dysfunction (r=0.35;p=0.003) than with volume of infarct (r=0.31;p=0.008). In multivariable regression, NIHSS was best predicted by infarct volume and hypoperfusion in each area ($F(7, 63)=3.95$;p=0.0012; $r^2=0.31$); independent predictors were infarct volume (t=2.18;p=0.033) and left MCA frontal hypoperfusion (t=2.91;p=0.005). In RH stroke NIHSS score correlated more strongly with volume of infarct (r=0.37;p<0.00001) than volume of tissue dysfunction (r=0.37;p=0.0005). In multivariable regression ($F(7, 78)=3.47$;p=0.0027;$r^2=0.24$) only infarct volume independently predicted NIHSS score (t=3.51; p=0.001), showing that NIHSS fails to capture penumbral tissue. Results support the hypotheses that (1) FHV rating can estimate total volume of dysfunctional tissue and that (2) in RH stroke, FHV rating may be more accurate than NIHSS score in estimating clinically significant hypoperfusion beyond the infarct (penumbra). Because penumbra identifies candidates for reperfusion therapies, results may have substantial clinical impact. Future studies will evaluate usefulness of this measure for identifying candidates for treatment outside of current time windows and for assessing reperfusion.

262. Appearance of Intracerebral Hemorrhage on Low-Field, Point-of-Care Magnetic Resonance Imaging

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Background and Aims: Advances in MRI technology have led to the development of a low-field (64mT), point-of-care (POC) MRI device. The appearance of intracerebral hemorrhage (ICH) on POC MRI has not been characterized. We aim to describe the appearance of ICH on low-field, POC MRI.

Methods: We studied 15 patients (47% female, ages 43-89 years) with a diagnosis of ICH confirmed by conventional imaging. T1-weighted (T1W), T2-weighted (T2W), and fluid-attenuated inversion recovery (FLAIR) fast-spin-echo exams were obtained on 12, 15, and 14 patients, respectively. Two patients were studied at two and four serial timepoints. Three raters analyzed 13 T1W, 19 T2W, and 18 FLAIR POC exams using a qualitative evaluation for lesion presence, location, and morphology. Signal intensity ratios (SIR) were computed by dividing the mean signal intensity of the lesion on a single slice by the mean signal intensity of the contralateral hemisphere. Averaged SIR and standard deviations were computed across raters.

Results: POC exams were acquired 13-210 hours (median=66 hours) after last known normal (LKN). Lesions were located in lobar (40%) and non-lobar regions (60%). Two lesions on T1W appeared isointense (SIR=1.00±0.05) with hypointense rim (0.68±0.18), eight lesions appeared hyperintense (1.26±0.09) with hypointense rim (0.70±0.06), and three lesions appeared as a homogenous hypointensity (0.80±0.20). Fifteen lesions on T2W appeared hypointense (0.83±0.09) with hyperintense rim (1.18±0.06), two lesions appeared isointense (1.01±0.01) with hyperintense rim (1.58±0.05), and two lesions appeared as a homogenous hyperintensity (1.17±0.07). Nine FLAIR exams appeared hypointense (0.86±0.07) with hyperintense rim (1.21±0.05), three lesions appeared isointense (0.98 ± 0.09) with hyperintense rim (1.31±0.03), and five lesions appeared as a homogenous hyperintensity (1.41 ± 0.07). Serial T1W POC exams for one patient studied at 45, 88, 111, 210 hours after LKN showed hemorrhage progression from an isointense to hyperintense lesion with hypointense rim. T2W and FLAIR serial exams demonstrated an evolving hyperintense rim consistent with conventional imaging. Serial POC exams for one patient studied at 23 and 48 hours after LKN demonstrated consistent appearance across serial scans, which aligned with conventional imaging.

Conclusion: These preliminary data inform appearance of ICH on POC MRI. Further work is needed to differentiate signal intensities across ICH progression and clarify the sensitivity and specificity of POC MRI.

263. Mortality Risk Stratification in Pediatric Ischemic Stroke: Analysis of 4,036 Inpatients in The United States

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Background: Pediatric ischemic stroke (PIS) is a rare but one of the leading causes of morbidity and mortality in young patients. The prevalence rate of PIS increased by 35% from 1990 to 2013.

Objective: To evaluate the in-hospital mortality risk in PIS due to cardiovascular and hematological risk factors.

Methods: We utilized the nationwide inpatient sample (NIS, 2010-2014) and included 4,036 inpatients (age <18) with a primary diagnosis of ischemic stroke. The sample was stratified by cardiovascular (CV, N=1,321), and hematological (HEM, N=1161) and no CV/HEM risk factors (N=1,554). Logistic regression was used to evaluate the impact of HEM and CV risk factors on odds ratio (OR) association with in-hospital mortality after controlling for demographics and potential risk factors.

Results: Most common CV risk factors in PIS included congenital abnormalities (51.1%), hypertension (25%), obesity (11.8%), and cardiomyopathy (8.7%), and prevalent HEM risk factors included systemic lupus erythematosus (SLE, 35.7%), sickle cell anemia (SCA, 26.2%), deficiency anemias (17.7%), and coagulation diseases (14%). Mortality rate was highest among CV-cohort compared to HEM-cohort (57.4% vs. 29.7%, P<0.001). Children (6-11 years, OR 2.3, 95%CI 1.43-3.73) and females (OR 1.2, 95%CI 0.84-1.76) had a higher mortality risk. When compared with no risk factors, HEM and CV was associated with four times (95%CI 2.36-8.03) and seven (95%CI 4.03-12.61) times higher odds for in-hospital mortality respectively. The most significant risk factors included cardiomyopathy (OR 15.6, 95%CI 9.19-26.56), diabetes (OR 11.2, 95%CI 5.01-24.86) and lymphoma/leukemia (OR 4.7, 95%CI 2.24-10.09) for in-hospital mortality in PIS.

Conclusion: CV and HEM risk factors increased the risk of in-hospital mortality in PIS by 613% and 336% respectively. Strategies should be developed for early screening and management of potential risk factors in at-risk populations to improve health-related quality of life in PIS.

264. Burden and Outcomes of Acute Ischemic Stroke among End Stage Renal Disease Patients: A National Perspective

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Background: Cerebrovascular accidents (CVA) like Acute Ischemic Stroke (AIS) are very common at all stages of chronic kidney disease (CKD) and associated with poor outcomes. CKD and End-Stage Renal Disease (ESRD) patients can be managed aggressively in the setting of acute stroke however prevention and prophylaxis for AIS are of uncertain benefit. Moreover, there is far less known regarding epidemiology and outcomes of AIS amongst ESRD individuals at the national level.

Objective: The study is aimed to determine the burden and the outcomes of AIS in patients on maintenance dialysis or ESRD from a nationally representative sample.

Methods: We derived the study cohort from the Nationwide Inpatient Sample (NIS) for years 2005-2016. Adult Hospitalizations with ESRD were identified using International Classification of Diseases (9th Edition) Clinical Modification diagnosis codes (ICD-9-CM) and ICD-10-CM diagnosis codes. AIS, other comorbidities, and complications were identified by using previously validated ICD-9-CM and ICD-10-CM diagnosis codes. We then utilized the Cochrane Armitage trend test and multivariate survey logistic regression to analyze temporal trends, predictors and outcomes.

Results: Out of a total of 9,274,014 hospitalizations of ESRD patients, 89,435 (1.0%) admissions occurred due to a primary diagnosis of AIS. Temporal trends over the study period remained stable. Amongst ESRD patients: Age (10-year increase) (OR 1.26; 95%CI 1.25-1.28; p<0.001), being uninsured (OR 1.23; 95%CI 1.16-1.30; p<0.001), female (OR 1.22; 95%CI 1.18-1.22; p<0.001) and individuals having comorbidities like hypertension, diabetes, congestive heart failure were significantly more likely to get admitted due to AIS. Moreover, ESRD individuals who admitted due to AIS had higher odds of in-hospital mortality (OR 2.00; CI 1.96-2.06; p<0.001) and discharge to specialized care (OR 1.88; CI 1.85-1.92; p<0.001).

Conclusion: Our study demonstrates the burden of AIS among ESRD individuals over the past decade. The risk stratification for the prophylaxis and poor outcomes requires to be assessed in future studies.

265. Corneal Confocal Microscopy: Corneal Nerve Loss in Acute Stroke Patients with Poor Pial Collaterals

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Stroke is a leading cause of death and disability around the world. Cerebral pial collaterals play a key role in determining outcomes by partially maintaining blood flow to ischemic cerebral tissue when primary conduits become occluded in stroke patients. The extent of collateral circulation cannot be predicted prior to the stroke and can only be assessed by CT angiography after a stroke has occurred due to major cerebral vessel occlusion. The rapid and non-invasive ophthalmic technique of corneal confocal microscopy (CCM) shows significant pathology of corneal nerves and endothelial cells in patients with acute stroke. We hypothesize that stroke patients with poor pial collateral circulation will demonstrate greater corneal nerve and endothelial cell damage when compared to stroke patients with moderate-good pial collateral circulation. 35 stroke patients with poor (n=12) compared to moderate-good (n=23) pial collaterals underwent corneal confocal microscopy and quantification of corneal nerve fiber density (CNFD), branch density (CNBD), fiber length (CNFL), fiber tortuosity (CNFT), endothelial cell density (ECD), area (ECA), perimeter (ECP), pleomorphism, and polymegathism. Age (52.42 $\pm$ 8.39 v 51.09 $\pm$ 11.60, p=0.73), BMI (p=0.92), cholesterol (p=0.69), triglycerides (p=0.76), LDL (p=0.69), and HbA1c (p=0.13) were comparable between the two groups, with the exception of systolic blood pressure (p=0.03). NIHSS showed a trend to be higher at admission (p=0.08) and discharge (p=0.07), and mRS was significantly higher at admission (p=0.01) in patients with poor compared to moderate-good collaterals. CNFL (16.26 $\pm$ 5.84 v 20.76 $\pm$ 5.22, p=0.03), CNBD (47.53 $\pm$ 30.04 v 72.89 $\pm$ 35.89, p=0.04), and CNFT (0.07 $\pm$ 0.03 v 0.10 $\pm$ 0.04, p=0.04) were lower with no significant difference in CNFD (28.07 $\pm$ 10.74 v 31.70 $\pm$ 6.85, p=0.23) and IWL (32.14 $\pm$ 5.45 v 33.93 $\pm$ 4.83, p=0.45) in patients with poor compared to moderate-good collaterals. There was a trend for lower ECD (2697.86 $\pm$ 386.66 v 2974.11 $\pm$ 346.57, p=0.15), and higher ECA (329.44 $\pm$ 44.37 v 297.71 $\pm$ 36.60, p=0.13) and ECP (66.67 $\pm$ 4.68 v 63.54 $\pm$ 3.90, p =0.16) in patients with poor compared to moderate-good collaterals. This study demonstrates greater corneal nerve pathology in patients with poor compared to moderate-good pial collaterals. CCM may represent a simple ophthalmic technique to define pial collateral status.

266. Optimizing the Evaluation and Treatment of In-Hospital Stroke

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Background: Up to 17% of acute strokes occur in patients hospitalized for another reason (Cumbler et al. Stroke 2010). Stroke-like symptoms may be difficult to appreciate, especially for non-neurology providers, due to the high incidence of stroke mimics (e.g. delirium) in the inpatient population (Cumbler et al. J Hosp Med 2015). Many centers have adopted inpatient-specific stroke protocols with the aim of improving time to diagnosis and treatment (Kassardjian et al.

Stroke 2017; Cumbler et al. J Stroke Cerebrovasc Dis 2010). We aimed to assess one of these instruments, the "2CAN" score (Chang et al. Stroke 2018), in our patient population.

Methods: A retrospective chart review was conducted for all inpatients for whom our Brain Attack Team (BAT) was called between January 2015 and June 2019. Patients were excluded if they had stroke prior to current admission, were in the ED at time of BAT call, or had incomplete documentation. Variables included timing of admission to BAT call, procedures received, medical history, medications, NIHSS, and whether the final diagnosis was stroke or stroke mimic. The 2CAN score was calculated for each patient.

Results: The BAT was activated 201 times, with 110 patients meeting inclusion criteria. Mean age was 61 (SD 14) and 46% were female. Twenty percent of patients had a history of A-fib, 72% HTN, and 36% DM. Median NIHSS was 15 (IQR 5-24). Only 10% of stroke calls occurred within 24 hours of hospital admission. 2CAN scores ranged from 0 to 5, with a mean of 2.8 (SD 1.2). Ninety-seven (88%) of patients received a final diagnosis of ischemic stroke and 13 (12%) of stroke mimic. There was no difference between 2CAN scores for the stroke and mimic groups ($P = 0.91$). A 2CAN score of ≥2 had sensitivity 83.5%, specificity 23.1%, PPV 89.0%, and NPV 15.8% for stroke in our cohort. A score of ≥3 had sensitivity 62.9%, specificity 30.8%, PPV 87.1%, and NPV 10.0%.

Conclusions: The 2CAN score was derived and validated in a single academic center as a tool for the non-neurology provider to recognize stroke. However, we were unable to achieve reproducibility of this score to the same degree in our academic center. Subsequent studies should continue to examine tools for the accurate identification and treatment of in-hospital strokes.

267. Horizontal Titibations with Alternating Movements

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Objective: To identify Horizontal titubations post cerebellar stroke.

Background: Classically described in Children with Joubert syndrome and as a drug reaction, horizontal titubations, are usually a manifestation post cerebellar vascular infarction as a vertical dyskinesia (1). Horizontal titubation's post infarct has not herefore been described.

Methods:

Case Study: This 66-year-old right-handed woman, four months prior to presentation had acute onset of loss of balance, recurrent falls with episodes of contusion without loss of consciousness. As she elevated, she became nauseous and vomited with the sensation of vertigo. With no improvement of symptoms, the patient was transported to the Emergency room. CT found that she had a right cerebellar hemisphere hemorrhage.

Results: Neurological examination: Cranial nerve examination: CN1: alcohol sniff test =5 (Anosmia). CN 2: pupils Anisocoria OD 4mm OS 3mm. Visual field with the Left minor hemianopia. CN 3,4, and 6 show CN6 palsy. Right sided ptosis. CN 8: Absent AU- to CALFRAST. CN11: Left sternocleidomastoid hypertrophy. At rest absent titubation in linear sitting. With rapid alternating movement of the fingers, horizontal titubation began and persisted through the rapid alternating movements. On extinction of rapid alternating movements, the titubation also ceased. Titubation: 3 -5 Hz/sec.

Conclusion: The exhibition of horizontal titubations shows a direct involvement of the cerebellar pathways dentorubro -thalamo-cortical / dentato-rubro-olivary pathways (3). The pathway interruption manifested itself as sternocleidomastoid, semispinalis capitis and the splenius capitis muscle bilaterally alternating spasms. This is an uncommon phenomenon as most cerebellar injuries present with vertical yes/yes if at all (2). Continually, inquiry would aid in the discovery of cerebellar to midbrain connection and the interaction of the tracts for voluntary movement. Specifying the interaction aforementioned maybe worthwhile for understanding the differences in involuntary tremors.

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268. The Influence of Metabolic Syndrome on Gray Matter Volume in Early, Young, and Middle-Aged Mexican-American Adults

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We investigated the relationship between biometric indices of Metabolic Syndrome (MetS) and gray matter volume (GMV) in brain regions that we previously identified as the "neural signature of MetS". The effects of age and sex also were examined across a large sample of adults, ages 18-65. Lipid profiles and biometric assessments were obtained from 776 Mexican-American participants who underwent magnetic resonance imaging (MRI) to quantify regional brain volumes. The components of MetS were derived from the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III). Subjects were grouped by age as follows: early adult (18-25 years), young adult (26-45 years), and middle-aged adult (46-65 years). Linear regression was used to identify relationships between MetS components (waist circumference [WC], fasting plasma glucose [FPG], triglycerides [TG], HDL cholesterol, blood pressure [BP],) and gray matter volumes in five brain regions previously linked to MetS: 1) cerebellum, 2) brainstem, 3) orbitofrontal cortex, 4) right insular/limbic cluster and 5) caudate. In both

men and women of each age group, WC was the most significant predictor of GMV across all 5 brain regions combined. In the early adult age group, effect sizes were larger in men (r^2 = .35) than women (r^2 = .18) ($p < .001$) whereas the inverse was true in middle-aged men (r^2 = .11) versus women (r^2 = .19). The single brain structure most closely associated with MetS was the posterior cerebellum.

269. Domain-Specific Cognitive Performance after Incident Stroke: The Northern Manhattan Study

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Greater cognitive decline after incident stroke has been previously well-documented, but domain-specific cognitive decline is underexplored. Additionally, estimates among racially/ethnically diverse samples are lacking, despite the fact that racial/ethnic disparities in stroke and dementia burden exist. Using data from the Northern Manhattan Study, we examined the change in domain-specific cognitive performance, as measured by a neuropsychological battery, using repeated measures ANOVA to examine change in cognitive function between two neuropsychological measurements in those with an incident stroke compared to those without an incident stroke. Episodic memory, semantic memory, processing speed, and executive function were measured as z-scores constructed by taking the mean of z-scores of individual neuropsychological exams that load onto each cognitive domain. Analyses were adjusted for age, sex, years of education, physical activity, smoking status, systolic and diastolic blood pressures, blood glucose, anti-hypertensive medication use, and anti-diabetes medication use, measured at baseline. There were 927 with neuropsychological data available. The sample was made up of 62% women, 68% Hispanic/Latino, 16% non-Hispanic Blacks, and 13% non-Hispanic whites. Of the 927 participants, 25 had an incident stroke during between an average of 5 years between the first and second neuropsychological exams. The sample had a mean age of 63 years (SD = 8) and mean years of education of 10 (SD = 5). Compared to those who did not experience an incident stroke, those who had an incident stroke exhibited a decline in performance in all domains except for executive function (β = -0.04, 95% CI = -0.26, 0.34). There was a decline in z-score units of episodic memory by -0.35 units (95% CI = -0.63, -0.07), semantic memory by -0.51 units (95% CI = -0.72, -0.31), and processing speed by -0.73 units (95% CI = -0.99, -0.47). Those who had an incident stroke between their first and second neuropsychological exams exhibited variable declines across most domains. The strongest association was observed for processing speed, consistent with previous work connecting cerebrovascular damage with declines in this domain. Larger studies are needed to examine differences between racial/ethnic groups and specific stroke type, location, and mechanism.

270. Could Ischemic Stroke Infarct Volume Aid in Determining Stroke Subtype?

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Background: Identification of stroke etiology facilitates proper treatment. The relationship between ischemic stroke infarct volume and stroke subtype is poorly understood, with size not necessarily indicating the cause of the stroke. We hypothesize that larger infarct volume is associated with cardioembolic stroke versus other subtypes, independent of risk factors that may affect the association between infarct volume and stroke etiology.

Methods: Inclusion criteria reflect those of a larger study: Johns Hopkins Hospital inpatient admission (2015-2019) for ischemic stroke with confirmatory brain MRI, and transthoracic echocardiogram. Infarct volumes were calculated using MRIcron© by a reviewer masked to participant characteristics. Ischemic stroke subtype was independently adjudicated by a cerebrovascular neurologist using Trial of Org 10172 in Acute Stroke Treatment (TOAST) classifications. Multivariable logistic regression was used to determine the association between infarct volume and one stroke subtype versus all others. Multinomial logistic regression was used to further compare the risk of cardioembolic stroke directly versus each other stroke subtype, per unit change in infarct volume. Stepwise adjustment accounted for potential confounders; Model 1: age, sex, black race; Model 2: Model 1+ body mass index, low density lipoprotein, hypertension, diabetes mellitus, smoking (ever vs never smoker).

Results: The participants (N=150) were on average 61 years old (range 18-98), male (58%), and black (57%). Per 5mL increase in infarct volume, there was a higher odds of cardioembolic stroke (odds ratio [OR] 1.07, 95% CI 1.01-1.14) and large-artery strokes (OR 1.10, 95% CI 1.02-1.18) in the final adjustment model. Per 5mL increase in infarct volume, there was a 82% decreased odds of having a small-vessel stroke versus other subtypes (95% CI 0.06-0.55, model 2). Risk of cardioembolic versus large-artery stroke was nonsignificant per 5mL increase in infarct volume (relative risk ratio [RRR] 1.01, 95% CI 0.94-1.09, base cardioembolic), whereas risk of cardioembolic versus small-vessel stroke was significantly decreased with larger infarct volumes (RRR 0.17, CI 0.06-0.53, base cardioembolic).

Conclusion: This single-center prospective cohort study demonstrated that larger infarcts had increased odds of both cardioembolic and large-artery strokes, with no difference when directly compared, as well as a decreased odds of small-vessel stroke. Additional work is ongoing to determine whether precise location and number of infarcts can help further distinguish among stroke etiological subtypes.

271. Stumped by Recurrent Strokes? Think of "Stump" Syndrome!

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Introduction: Following an arterial occlusion, further ischemic events are not expected as the occluded vessel is without flow. Vertebral artery stump syndrome (VASS) is an exception to this reasoning. When a thrombus occludes the proximal vertebral artery, embolization of the distal portion of the clot can result in new thromboembolic events.

Case Description: A 55-year-old man with hypertension, dyslipidemia and diabetes mellitus presented with gait instability, left upper extremity (LUE) dysmetria and left-sided facial numbness. Computed tomography angiography (CTA) of the head and neck showed left vertebral artery (VA) occlusion at its origin, with distal reconstitution at the C4-C5 level. Magnetic resonance imaging (MRI) of the brain showed ischemic strokes in the left inferior cerebellum and adjacent medulla. Transthoracic echocardiogram did not reveal any source of cardioembolism. The patient was placed on aspirin and atorvastatin. Three weeks later, he developed new symptoms and signs. There was now left homonymous hemianopia and mild left sensori-motor weakness. CTA of the head and neck showed progressive occlusion of the left vertebral artery, now with distal reconstitution at the C2 level and new occlusion of the right posterior cerebral artery (PCA). MRI of the brain showed an acute infarct superimposed on the previous left cerebellar infarct, along with new infarcts in the bilateral occipital lobes, inferomedial temporal lobes, and right thalamus.

Discussion: Various theories have been suggested to explain VASS: low flow state, emboli of distal clot fragments, and clot migration through collaterals (deep and ascending cervical arteries, occipital artery). This case illustrates how recurrent strokes can occur in posterior circulation territories, despite a persistent vertebral artery occlusion. Clinicians need to be aware of this dangerous phenomenon when caring for patients with vertebral artery disease.

272. Adapting Reach Out: A Mobile Health Intervention Trial, in Response to the Coronavirus Pandemic

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Background: Hypertension is the most important modifiable risk factor for stroke and an important contributor to the racial disparities of stroke. The Emergency Department (ED) may represent an opportunity to reach difficult-to-reach hypertensive populations. We discuss how we adapted a mobile health behavioral intervention during Michigan's stay-at-home order in response to the coronavirus outbreak.

Methods: Reach Out is a health system focused, multicomponent, health theory based, mobile health behavioral intervention to reduce blood pressure (BP) among ED patients at a safety net hospital in the under-resourced, minority, majority community of Flint, Michigan. The primary outcome is change in systolic blood pressure at twelve months. Outcome assessments are conducted at six months and twelve months, during which BP is measured. The 6 and 12-month outcome assessments include surveys and blood pressure measurements. Prior to COVID-19 these assessments were conducted in-person at various locations throughout the community that were convenient for each participant. During an in person assessment, the survey would be completed and a total of 3 blood pressure measurements would be taken in a timed sequence.

Results: In response to the Coronavirus stay-at-home orders, we transitioned our in-person outcome assessments to tele-outcome assessments. The surveys were conducted over the phone. BP were taken by participants with their study provided home BP cuff. To increase the validity of the home BP assessments, participants are asked to send pictures of BP cuffs being worn in accordance with instructions (but not including other identifiers) and 3 BP measurements reported to the study team through text message or phone call. Prior to COVID-19, in-person outcomes were conducted from 10/4/2019 to 3/13/2020. Within this timeframe, 93 of 290 (32%) possible in-person outcomes were completed. Tele-outcomes commenced on 4/9/2020 to 5/28/2020. Since beginning 111 of 323 (34%) tele-outcomes have been completed.

Conclusion: Flexibility and versatility are essential when retaining participants in an ongoing clinical research trial. It is even more vital to keep this in mind when working to retain participants from more vulnerable populations. Reach Out's innovative transition to tele-outcome assessments for data collection has proven to be just as productive as in-person assessments. The results also imply that this new process could help increase the retention rate in future trials.

273. Cardiac Structure and Function is Associated with Hemispatial Neglect Severity

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Background: Hemispatial neglect can occur in right hemispheric stroke, with evidence that patient-level factors influence neglect severity. Whether cardiac structure and function, perhaps by altering perfusion and stroke recovery, is associated with worse neglect is unknown. In this single center study of acute ischemic right hemispheric stroke patients, we hypothesized that markers of worse cardiac function would be associated with presence and severity of hemispatial neglect, independent of infarct size.

Methods: Inclusion criteria were nondemented patients with acute ischemic right-hemispheric stroke (RIS) with diffusion weighted imaging magnetic resonance imaging (DWI) and echocardiography admitted to Johns Hopkins who completed ≥1 cognitive test evaluating neglect (N=218). Four tests (Horizontal Line Bisection, Line Cancellation, Copy Scene, Big Gaps) defined neglect using age- and sex-based Z-scores. Neglect severity for those with ≥2 tests was

categorized as no neglect, neglect on 1/4 or neglect on 2 or more of 4 tests. The dependent variable was presence of neglect (any vs none; multivariable logistic regression), or neglect severity (multinomial logistic regression). The association with prespecified cardiac features of left ventricular structure/function (independent variable) was evaluated using separate nested adjustment models (Model 1: demographics, atrial fibrillation; Model 2: Model 1 + education, DWI volume).

Results: Patients were on average 61yo (21-95), female (50%), black (53%), hypertensive (76%) with an ejection fraction (EF) of 60% (IQR 20%-75%). 58/218 had neglect. There was no significant association between each of the cardiac variables of interest and the dichotomous outcome (presence of neglect) in separate models. However, a 1cm increase in LV systolic diameter was associated with a higher relative risk of having neglect on 2 tests compared to those with no neglect (reference) (RRR=1.83, 95%CI 1.01-3.32), but not after adjusting for education and DWI volume (RRR=1.68, 95%CI 0.89-3.19). Per 1cm increase in left atrial (LA) diameter, the relative risk of having neglect on 2 tests versus no neglect was two times higher (RRR=2.23, 95%CI 1.04-4.77), but again lost significance in the final model (RRR=1.73, 95%CI 0.76-3.94).

Conclusions: In a single-center cohort of RIS, we found an association between markers of diastolic dysfunction (enlarging LV, compensatory enlarging LA) and severity of neglect, defined as more frequent neglect on different cognitive tests. As associations were no longer significant after adjustment for infarct volume, this emphasizes the importance of considering stroke etiology and size when evaluating neglect and other cognitive deficits post-stroke.

274. Asymptomatic Giant Tumefactive Perivascular Spaces- An Incidental Finding

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Background: Giant Tumefactive Perivascular Spaces (GTPVS) is a rare pathology occurring due to abnormal enlargement of Virchow-Robin spaces of the brain.

Objective: The aim of this article is to provide a descriptive review of GTPVS; with an illustrative case report.

Illustrative Case Report: A 79-year-old female, with a past medical history of hypertension, atrial fibrillation, and hypothyroidism presented with complaints of gradually progressive bilateral asymmetric hearing loss of 7 years duration and saw an ENT specialist because of worsening symptoms over the last 6 months. She denied any headaches, vision changes, balance difficulties or any motor weakness; and her neurological examination was non-focal, other than the bilateral sensorineural deficit. An audiogram showed a bilateral sensorineural hearing loss, worse on the left than right. Magnetic Resonance Imaging (MRI) of her brain revealed multiple non-enhancing cystic lesions in the right basal ganglia, thalamus, temporal lobe, and cerebral peduncle, with minimal mass effect on the third ventricle, consistent with prominent perivascular spaces. She was referred to Neurology and was managed conservatively.

Review Method: A literature search was done on PubMed using the keyword 'Giant Tumefactive Perivascular Spaces'. Studies in the English language reporting the clinical presentation, diagnostic workup, and treatment of GTPVS were descriptively analyzed for our review.

Review Results: 1. GTPVS are rare lesions that can be frequently misdiagnosed as intracranial cystic neoplasms and are commonly found in the mesencephalo-thalamic region. 2. The exact mechanism of enlarging perivascular spaces is still unknown, though multiple hypotheses have been proposed. 3. Vision changes, vertigo, balance difficulties, impaired cognitive function, and seizures have been found to be the most common complaint. 4. MRI is considered the most accurate form of imaging that shows single or multiloculated lesions with signal intensities identical to CSF in all pulse sequences. 5. Surgical intervention is preferred in patients who develop obstructive hydrocephalus and conservative management is considered in those who are asymptomatic.

Conclusion: GTPVS are abnormally enlarged perivascular spaces with a poorly understood etiopathogenesis and unknown prevalence. These lesions may produce a multitude of clinical signs and symptoms through mass effect. MRI is the gold standard for diagnosis. Symptomatic patients undergo surgery while asymptomatic patients require routine follow-up with imaging to watch for both new lesions, monitor the size of old lesions, as well as assess the progression of hydrocephalus.

275. Regional Assessment of Cerebral Microvascular Disease (RACMD) Score: A Clinical MRI Grading System

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Introduction: White matter abnormalities on magnetic resonance imaging (MRI) reflect cerebral microvascular disease (CMD) and independently double the risk of mortality per standard deviation difference. Highly related lacunar infarcts and Cerebral Micro-Bleeds (CMBs) correlate with clinical sequela such as stroke, dementia, myocardial infarction (MI) and death, making accurate measurement of CMD a central issue in cerebrovascular health. "Total Small Vessel Disease (SVD) Score" is currently the reference standard for clinical measurement of small vessel disease burden and has been correlated with outcomes such as dementia. Total SVD score, does not address the full spectrum of severity and varying pathophysiology of its components (i.e. white matter T2 hyperintensity, CMBs, lacunar infarcts, and dilated perivascular spaces). We aimed to develop a new grading system based on routine clinical brain MRIs and to compare the new scoring criteria against the total SVD score and Fazekas score.

Methods: A retrospective database search was performed to identify patients undergoing brain MRI in 2016. Clinically relevant patient characteristics and hard outcomes including all-cause mortality were abstracted from medical records. We applied our grading system "RACMD Score", total SVD score and Fazekas score to these MR images (T1, T2, T2-FLAIR, GRE, and DWI sequences). "RACMD Score" incorporates neuroanatomical localization of lesion burden and type with a maximum score of 9 and assigns 0-3 points to 3 categories. CMBs, lacunar infarcts, and white matter T2 Hyperintensities are divided into strictly lobar (1 point), deep (D) or infratentorial (I) (2 points), and combined lobar and D/I (3 points). We performed logistic regression of all three grading systems, adjusted for age, with a dependent variable of all-cause mortality. ROC curves were also graphed for each logistic regression analysis.

Results: A total of 46 (44 Males) veteran patients (age range: 66-93, mean 74.6, median age: 71) were included. Comorbid conditions included 39% diabetes, 76% hypertension, 65% dyslipidemia. Based on ROC analysis with comparison of AUC, "RACMD score" performance score is superior to "total SVD score" and "Fazekas" (0.75 vs 0.73 vs 0.67). "RACMD score" results in a statistically significant model fit (P-value < 0.05), while the other two grading systems do not.

Conclusion: Incorporation of regional variation in the diagnostic evaluation of CMD including microbleeds and lacunar infarcts improves the imaging evaluation of CMD and associates with all-cause mortality in a limited sample of at-risk, predominantly male veterans.

276. Altered Brain Network Dynamics in Stroke Predict Behavior

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Stroke causes both local alterations of function in the area of structural damage as well as remote network effects on directly and indirectly anatomically connected areas, which can be measured with resting state functional connectivity (FC). Previous results defined robust static FC biomarkers of stroke impairment: a decrease of homotopic inter-hemispheric within-network connectivity, and an increase of intra-hemispheric between-network connectivity (He et al, Neuron, 2007; Carter et al, Ann Neurol, 2010; Siegel et al, PNAS, 2016). Some results suggest that these FC alterations correspond to a decrease of the variability of spatial neural patterns (Siegel et al, Cortex, 2018; Adhikari et al, Brain, 2017). However, functional interactions among regions are not static, but vary over time. Therefore, it is unknown whether stroke also causes alterations in the dynamics of functional interactions.

Subjects: n=47 first-time stroke subjects, studied at 2 weeks, 3, and 12 months, and n=20 age- and education-matched control subjects studied twice 3 months apart, with structural and diffusion MRI, resting-state fMRI, and a large battery of behavioral tests. Dynamical functional states (DFSs): DFSs represent snapshots of FC computed through a sliding-windows approach (duration 60 sec, step 2 sec), and then clustered with time-wise K-means clustering carried out over all subjects (controls and patients at each time point). Hence each sliding window for each subject is characterized by the activation of a specific DFS, whose dynamic is described in terms of frequency of occurrence, averaged life span, and transition probability. Significant differences in terms of these dynamical measures were tested across populations, in order to identify abnormal patterns of states activity in acute stroke, which possibly recovered after 3 or 12 months (chronic stage).

Results: Stroke did not cause the emergence of unique DFSs, rather some DFSs were significantly more present at the acute stage and recovered over time. Patients with more or less severe impairment of static FC had correspondingly greater impairment of dynamical states. A model-based analysis showed that dynamical abnormalities were related to specific lesion topography. Finally, DFSs abnormalities explained part of the behavioral deficits' variance, which was not explained by static FC.

Conclusions: Dynamical FC analysis reveals network abnormalities that go beyond network topography. This relatively simple description could be the basis for the development of a mathematical model aimed at optimizing real life neurostimulation to rebalance patterns of altered static and dynamic FC.

277. Association between Hematoma Characteristics and Risk of Uncontrolled Blood Pressure in Intracerebral Hemorrhage Survivors

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Background: Uncontrolled blood pressure (BP) in intracerebral hemorrhage (ICH) survivors is common and associated with increased risk for ICH recurrence. Information available during acute hospitalization that predicts poor BP control in follow-up could be used to improve management of this population. In this study we sought to investigate whether baseline hematoma characteristics are associated with follow-up BP levels in ICH survivors.

Methods: Subjects were consecutive patients aged ≥ 18 years with CT-confirmed ICH, recruited prospectively

for a single-center longitudinal study at Massachusetts General Hospital from July 1994 to December 2015. Our primary outcome was uncontrolled BP at 6 months, defined as BP ≥ 140/90 mmHg. Logistic regression models were constructed to investigate the association between ICH characteristics (ICH location, ICH volume) and uncontrolled BP, with potential confounders ($p<0.1$ in univariate models) adjusted for in multivariate models. False discovery rate (FDR) was applied to adjust for multiple hypothesis testing.

Results: 1344 patients were available for analysis, of whom 722 (53.7%) were males and 1145 (85.2%) were white; median age was 72 (IQR, 62-80) years. There were 679 (50.5%) ICH survivors with deep, 563 (41.9%) with lobar, and 102 (7.6%) with cerebellar ICH. Median ICH volume was 10 (IQR, 3.5-22.5) ml. At 6 months, 841 (62.6%) patients had uncontrolled BP; in the uncontrolled group, median SBP was 144 (IQR, 141-148) mmHg and median DBP was 84 (IQR, 81-90) mmHg. In univariate models, survivors of deep ICH had lower odds of uncontrolled BP (OR 0.78; 95% CI: 0.62-0.97, FDR=0.038), while patients with lobar ICH had higher odds of uncontrolled BP (OR 1.35; 95% CI: 1.08-1.69; FDR=0.029), compared to all other patients with ICH. ICH volume was not associated with risk of uncontrolled BP (OR 1.00; 95% CI: 0.99-1.00; FDR=0.61). After controlling for confounders, only lobar ICH was associated with increased odds for uncontrolled BP (OR 1.36; 95% CI: 1.07-1.71; FDR=0.032).

Conclusion: In a cohort of ICH survivors, lobar ICH was associated with increased risk for uncontrolled follow-up BP. Future studies leveraging biological and/or behavioral factors associated with uncontrolled BP could identify populations for more aggressive antihypertensive management.

278. Hippocampal Cellular Changes in the Three-Vessel Model of Global Ischemia in Rat

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Introduction: The hippocampus is one of the most vulnerable neuroanatomical regions that respond to hypoxia during ischemic event. Many studies confirm role of the hippocampus in the formation of long-term memory, therefore, it is important to understand processes that occur in the hippocampus, especially in the CA1 field, which is most vulnerable to ischemia.

Purpose: To study cellular changes including neuronal loss, demyelination, astrogliosis, and inflammation in the layers of the hippocampus after modeling three-vessel global cerebral ischemia (GCI) in rat.

Methods: Nine Wistar rats underwent GCI by transient occlusion of the main branches of the aortic arch. Sham-operated animals were used as controls. Animals were euthanized at days 11 and 31 after surgery. Brain sections were immunostained for mature neurons (NeuN), myelin (MBP), astrocytes (GFAP), oligodendrocyte progenitors (NG2), and microglia (Iba1). Cellular changes were explored in all hippocampal layers separately: St. oriens (SO), St. pyramidale (SP), Subst. radiatum (SR), Subst. moleculare (SM), and Subst. lacunosum (SL).

Results: 10 days after GCI, the number of mature neurons in the CA1 field decreased significantly ($p<0.001$) compared to controls only in SP. Neuronal loss was accompanied by an increase in microglia in all layers of the hippocampus within the CA1 field ($p<0.001$), except for SM. In SP and SL all Iba1+ cells had round-like morphotype of activated microglia whereas in SR microglia had rod-like morphology. MBP-positive area showed a decrease in SO ($p<0.01$), SR ($p<0.05$), and SM ($p<0.05$). Elongated bodies of Iba1+ cells in SR were oriented in the same direction as the myelinated processes of neurons and contacted with them. Astrogliosis was observed in SO, SP, and SR ($p<0.05$). The number of oligodendrocyte progenitors (NG2+ cells) was increased in SP ($p<0.05$). 30 days after GCI the number of neurons decreased compared 10-day time point in field CA1 ($p<0.05$). However, despite ongoing inflammation and astrogliosis, these animals show a tendency to recovery, which manifests itself in an increase in the number of NG2+ cells in all layers of the hippocampus in the CA1 field, except for SM ($p<0.05$).

Conclusion: GCI leads to astrogliosis, axonal demyelination, microglia utilization of myelin, and prolonged neuronal loss in the CA1 field of the hippocampus. Despite persistent inflammation, the first sign of recovery was an increase in the number of NG2+ cells in the CA1 field.

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279. The Need for Advanced Neuroimaging in Acute Ischemic Stroke: Lessons from a Multi-Year Retrospective Analysis at a Comprehensive Stroke Center

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Only 2-5% of the 650,000 people who have an ischemic stroke each year receive intravenous tissue plasminogen activator (tPA). Despite its multiple contraindications, a large majority of acute stroke patients are eligible for tPA therapy, but treatment is often withheld because of unknown or unreliable last well known times (LWKT). Recent studies, including MRWitness, WAKE-UP, EXTEND, suggest that using diffusion-FLAIR mismatch when LKWT is unclear correlates with higher 90day poststroke functional outcomes while having no difference in rate of post-tPA intracranial hemorrhages or associated disability. We conducted a retrospective review of 1,016 patients who presented with acute ischemic stroke to a single certified comprehensive stroke center. NINDS exclusion criteria were used to identify patients eligible for tPA therapy. Of the 1016 patients who presented with acute ischemic stroke, 125 patients (12.3%) received tPA, 58 patients (5.7%) received mechanical thrombectomy (MT), and 40 patients (3.9%) received tPA

plus MT. Of the remaining 793 patients who did not receive tPA or MT, 632 patients (79.7%) were excluded for having at least one contraindication (380 patients), having NIHSS<4 or rapidly resolving deficits (246 patients), or because of the patient's refusal (6 patients). There were 161 patients (18.9%) who were tPA eligible, but were excluded because of an unknown or unreliable LWKT. Comparing this group (n=161) to those who received tPA or tPA plus MT (n=125) revealed no differences in gender (no tPA: 68 females, tPA: 81 females, p=0.9999), age (no tPA: mean 69.9, tPA: mean 71.3, p=0.3058), race (no tPA: 62.1% white and 37.9% other, tPA: 58.8% white and 41.2% other, p=0.3588), NIHSS score at arrival (no tPA: mean 12.9, tPA: mean 10.6, p=0.3061), or the number of hospital days (no tPA: mean 6.2 days, tPA: mean 5.0days , p=0.9542). Our retrospective analysis of 1016 patients who presented with acute ischemic stroke revealed that a large group of 161 patients (15.8%) were eligible for tPA but did not get the therapy because of unknown or unreliable LKWT. There were no differences in demographic characteristics between this group and those who received tPA, thus adding evidence to prior studies in suggesting that use of advanced neuroimaging may expand the use of tPA and decrease poststroke morbidity. Implications of these findings on resource allocation and patient care in a comprehensive stroke center are further discussed.

280. A Case of Transient Cerebral Edema Following Endovascular Repair of Basilar-Tip Aneurysm Using Double-Catheter Technique

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Background: Basilar apex aneurysms constitute 5-8% of all intracranial aneurysms. A well-known technique using a double-catheter approach is often utilized to treat those with a wide-neck (>4mm). Here, we present a case of a patient with basilar apex aneurysm who developed transient encephalopathy following stent-assisted coiling.

Case presentation: A seventy year-old man presented for elective repair of an unruptured 4x4x5 millimeter basilar apex/left posterior cerebral artery, P1 segment aneurysm, achieved with a double-catheter technique with bilateral access through common femoral arteries. LVIS Jr 3x17 millimeter stent was deployed across the neck of the aneurysm with subsequent coiling with 4x5 centimeter Hydroframe, Hydrosoft-10 and MicroPlex coils. Simultaneous injection of contrast was administered through the guided catheter within the left internal carotid artery and the right vertebral artery. Several hours following an apparent uncomplicated procedure, the patient developed disorientation and agitation. Neurological examination was remarkable for global aphasia, which over next few hours improved to receptive aphasia. CT head without contrast and CTA head and neck showed sulcal effacement and cerebral edema of the left hemisphere, but no significant intracranial large vessel stenosis or occlusion. MRI brain performed the next day did not show any acute infarct or hemorrhage. There was significant improvement in the left hemispheric cerebral edema. Continuous EEG showed intermittent focal slowing over the left hemisphere without any epileptiform discharges or electrographic seizures. He was treated with a short course of steroids with resolution of neurological deficits over 48 hours. He was asymptomatic at the time of discharge from the hospital.

Discussion: We propose two possible mechanisms for the development of transient cerebral edema in this patient. The first is iodinated contrast associated encephalopathy with preferential left hemispheric involvement due to selective catheters placement. This entity's incidence is about 2.9%, with increased risk associated with double-catheter technique and simultaneous contrast injections. This rare and partially understood complication of neurovascular interventions is thought to be due to reversible dysfunction of the blood-brain barrier induced by repeated contrast injections. The second mechanism is transient focal cerebral hypoperfusion due to placement of large-bore catheter in the left ICA for extended period during the procedure, followed by sudden reperfusion upon removal, which could lead to cerebral hyperperfusion syndrome. This rare complication should be considered in evaluating patients with neurological symptoms following endovascular procedures.

281. The Low Dimensional Structure of Neurological Impairment in Stroke

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Neurological deficits are traditionally described in terms of syndromes related to either the damage of a specific area (e.g. Broca's area) or a vascular distribution (e.g. a left middle cerebral artery stroke). Recent studies however indicate that neurological deficits post-stroke are best described at the population level by a set of deficits that are correlated across different functional domains (i.e. motor, vision, language, memory, attention)(Corbetta et al. Neuron 2015), and that relate to the dysfunction of distributed brain networks (Siegel et al. PNAS 2016). To examine the reproducibility and specificity of this structure of impairment, and its underlying lesion anatomy, we studied a population of prospective first-time stroke individuals at the University Hospital of Padova, Italy, using a brief and clinically applicable neuropsychological assessment, and compared behavior and anatomy with those obtained on a different prospective cohort at Washington University in St. Louis.

Subjects: A prospective sample (n=159) of first-time stroke patients was studied at one-week post stroke (5±3.3 days post-stroke) with the Oxford Cognitive Screen (OCS) and the National Institutes of Health Stroke Scale (NIHSS). A principal component analysis was used to reduce variables

and describe the variability of behavioral deficits across patients. Lesions were manually segmented on structural scans (MRI/CT), and the relationship between anatomy and behavior was analyzed using multivariate ridge regression models.

Results: Three principal components (PC) of impairment explained ≈50% of the behavioral variance across subjects. PC1 loaded on language and memory deficits (27%); PC2 loaded on left side motor, visual, egocentric neglect, and overall performance deficits (13%); and, PC3 loaded on right side motor deficits and right egocentric neglect (9%). These components matched those obtained in St. Louis with a more extensive neurobehavioral battery. The underlying lesion anatomy in the two cohorts were also similar.

Conclusion: Neurological deficits following stroke are highly correlated across domains in a low dimensional structure of impairment, which is related neither to the damage of specific area or the vascular distribution, rather they reflect widespread network impairment caused by focal lesions. These factors represent robust behavioral biomarkers for future behavioral and treatment studies at the population level.

282. Diffusion: Not All Diffusion Restrictive Lesions on MRI Suggest an Acute Infarct

***Ayush Singh, MD**, Neeharika Thottempudi, MD, Chilvana Patel, MD, Hashem Shaltoni, MD, Anand Patel, MD. UTMB, Galveston, TX, USA.*

Introduction: Magnetic resonance imaging (MRI) is the most commonly used modality to evaluate for an acute infarct seen as a diffusion restriction (DR) lesion. Apart from an acute infarct, DR is described with epidermoid cyst, abscess, meningioma, chordoma as well as with Crutzfeld-Jaboc disease etc. Wallerian degeneration occurs due to demyelination of the distal neuronal axons due to proximal damage of any etiology. Here we report two stroke cases demonstrating DR as a marker of Wallerian degeneration.

Cases: Case 1 is a 47-year-old right-handed man with hypertension who was admitted to the hospital with decreased level of consciousness and quadriparesis, due to an acute pontine infarct secondary to mid-basilar thrombosis. Following his discharge to rehab, he was re-admitted to hospital for worsening of his neurological deficits. Follow up MRI brain (18 days later) showed expected evolution of the prior pontine infarct but also showed new symmetric diffusion restrictions involving bilateral middle cerebellar peduncles consistent with Wallerian degeneration.[1] Case 2 is a 56-year-old right-handed woman with hypertension, diabetes mellitus and prior ischemic stroke with residual left hemiparesis, who was admitted to the hospital with right leg weakness and abulia, due to left anterior cerebral artery (ACA) distribution stroke. About 2 weeks later, she was re-admitted to the hospital with toxic-metabolic encephalopathy. Repeat MRI brain showed expected evolution of the left ACA distribution infarct but in addition showed a new focus of diffusion restriction in the left internal capsule with T2/FLAIR hyperintense signal extending in to left cerebral peduncle representing changes consistent with Wallerian degeneration.

Conclusion: Wallerian degeneration follows an acute stroke and is seen on MR imaging as diffusion restriction. Here we propose careful interpretation of the MR imaging especially when performed in the subacute phase as new diffusion restriction noted in the neuronal pathways of recent acute infarcts would likely represent Wallerian degeneration and not a new acute ischemic lesion, which has both diagnostic and treatment implications. With more frequent use of MR imaging, further observations to support our findings are proposed.

283. Challenges and Approach to the Diagnosis of Spinal Cord Infarction

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Background: Spinal cord infarction (SCI) comprises 0.5-1% of all strokes and is usually seen as a sequela of trauma or aortic surgery. SCI remains a diagnosis of exclusion in cases without an obvious precipitating event because of its wide range of clinical presentation and lack of a specific diagnostic test.

Case Description: 56-year-old Caucasian previously healthy woman presented to our hospital for evaluation of 1-day history of rapidly progressively bilateral lower extremity weakness. Initial examination was positive for paraparesis with 3/5 to 4/5 strength in lower extremities, preserved reflexes, sensations, coordination and cranial nerves. On day 2 of hospitalization, symptoms rapidly progressed resulting in complete loss of strength in bilateral lower extremities, absent reflexes, absent pinprick and temperature sense, and urinary retention. MRI spine showed non-enhancing, linear T2-hyperintensity in anterior spinal cord bilaterally extending from T3-T5 levels in thoracic cord. CSF studies were significant for elevated protein but negative for viral, bacterial, mycobacterial or fungal infections. Serology was negative for AQP4-IgG, ANA, SS-A, SS-B, factor V Leiden, and ACE. Nutritional work-up was negative for vitamin deficiencies. Due to imaging result, patient was suspected to have SCI. CT angiography did not show aortic disease. She was treated with IV methylprednisolone 1000 mg for 5 days and 5 sessions of plasma exchange without significant improvement. However strength improved significantly after a few months.

Discussion: MRI can be helpful in excluding a compressive myelopathy. Confirmatory Spinal MRI DWI sequence has its own limitations and SCI is largely a clinical diagnosis of exclusion. Vascular imaging, including MR angiography can exclude Aortic disease. Spinal angiography remains the gold standard procedure but is complex to perform and is not readily available at all institutions. Cerebral spinal fluid analysis can exclude infectious and inflammatory myopathies. Following this approach we were able to diagnose SCI with significant confidence.

284. Dietary Supplements in Stroke Prevention: A Review of Recent Literature

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Improved nutrition after ischemic or hemorrhagic stroke promises to reduce stroke recurrence by indirect effects on diabetes, hypertension, and coronary artery disease as well as

direct effects of dietary supplements on stroke pathophysiology. While medications to prevent stroke have been thoroughly researched, much less is known regarding the impact of dietary supplements. Here we review the literature on the effects of multivitamins, chocolate, coffee, green/black teas, fish oil, fats/cooking oils, and dietary fiber on secondary stroke prevention. As a result, we find that teas, coffee, dietary fiber, and chocolate may offer significant reductions in stroke incidence.

285. Cerebral Air Embolism Complicating Atrio-Esophageal Fistula in Williams Syndrome

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Background: Cerebral air embolism (CAE) is a rare cause of stroke with unknown incidence. In 77.8% of reported cases, CAE is preceded by iatrogenic instrumentation of the systemic or cranio-cervical vasculature. We describe a case of acute stroke due to CAE that complicated percutaneous cardiac ablation for atrial fibrillation (AF).

Case Summary: A 53 year-old man with history of Williams syndrome and AF underwent elective intra-cardiac pulmonary vein isolation (PVI) to control ectopy. Twenty-five days later, the patient incurred a brief episode of syncope and right gaze deviation. After a second episode, he presented to hospital and was febrile (102.4°F) with hematemesis. Initial CT brain scan was unremarkable. After a third episode of right gaze deviation and right hemiparesis, the patient had respiratory arrest and was intubated. Repeat CT scan demonstrated diffuse pneumocephalus, severe cerebral edema, and transtentorial herniation. Air was present within some intracranial vessels. Blood cultures were positive for multiple streptococcus species.

Discussion: Williams syndrome, caused by gene deletion within the Williams-Beuren critical region at 7q11.23, is associated with elastin arteriopathy (EA) in 75% of cases. At autopsy, our patient was found to have an atrio-esophageal fistula (AEF) with an endocardial thrombus. We suspect that our patient had EA and may have been susceptible to developing AEF after PVI. Cause of death for our patient was shown to be bacterial endocarditis with systemic air and infectious emboli. Stomach contents were found within the intra-luminal space of cerebral arteries. Our patient was affected by a triad of symptoms attributed to AEF (fever, hematemesis, and neurological deficit), which is reported to occur 3 - 41 days after cardiac ablation. Air embolization is an extremely rare complication of cardiac ablative procedures, described in only 0.01 - 0.2% cases by percutaneous approach. Chest CT is needed to confirm AEF after cardiac ablation, when suspected.

Conclusion: Cerebral air and infectious embolization due to AEF should be considered when confronted by delayed neurological complication after cardiac ablation.

286. Lateral Lesion: A Case of Wallenberg Syndrome

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Introduction: Wallenberg Syndrome (WS) is an infarction of the lateral medulla that due to ischemia of the posterior inferior cerebellar artery (PICA).

Case: The patient is a 46 y/o M with no significant past medical history presented for a 2-day history of choking. While consuming candy he began having difficulty swallowing candy and subsequently his saliva. In addition, he noted right upper extremity numbness. In the ED, Vital signs were 152/80, HR 75, RR 19 with oral temp of 98.5. Routine labs revealed leukocytosis of 14.4. Physical exam revealed dysphagia and left pupillary miosis, left sided ptosis and diminished pinprick over the right arm. NIHSS score was calculated to be 3. CTA of the neck showed some prominence of the left aryepiglottic fold and somewhat unusual appearance of the anterior aspect of the vocal cords. MRI of the brain revealed small focus of restricted diffusion in the left medulla compatible with infarct. The patient was admitted to the stroke service, and placed on aspiration precaution. Patient was started on risk modification therapy and was seen by speech and swallow who initially felt the patient needed to be NPO due to severe cough and regurgitation during swallow trial. However, prior to discharge the patient tolerated a dysphagia puree diet.

Discussion: Wallenberg Syndrome is an infrequent cause of cerebrovascular accident. This syndrome occurs when the PICA becomes infarcted causing a particular constellation of neurological deficits in patients. Theses deficits include ipsilateral Horner's syndrome (miosis, ptosis and anhidrosis) with contralateral loss of pain and temperature in the limbs and trunk. Bulbar muscle weakness occurs from loss of supply to nucleus ambiguous, it is found in over 50% of patients with WS. This lesion can lead to paralyses causing dysphagia as seen in our patient. In patients with suspicious signs and symptoms on physical exam; an MRI confirms the location of the infarct. If the patient presents within 4 hours of symptoms onset tPA can be administered. Outside of this window the patient can be monitored and provided with risk factor modification therapy. Occupation and Physical therapy are also mainstays of treatment to attempt recovery of functionality after stroke.

Conclusion: Wallenberg syndrome is often missed by primary practioner thus knowing the common signs and symptoms should always be recalled when assess patient with acute neurological deficit.

Reference: Lui F et al, Wallenberg Syndrome. 2020 Jan. https://www.ncbi.nlm.nih.gov/books/NBK470174/

287. Reversible Cerebral Vasoconstriction Syndrome in a Patient Sprayed by Oleoresin Capsicum "Pepper Spray"

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Background: Reversible Cerebral Vasoconstriction Syndrome (RCVS) is radiographically characterized by multifocal

smooth narrowing of cerebral arteries with clinical manifestations ranging from a self-limited thunderclap headache to potentially catastrophic hemorrhagic and ischemic strokes, cerebral edema, and death in rare cases. Dysregulation of cerebrovascular tone is the prominent mechanism leading to RCVS, which can be induced by various mechanisms such as sympathetic overactivity, endogenous catecholamines, estrogen, endothelial dysfunction, and a host of exogenous ligands. Pepper Spray is employed worldwide as a non-lethal incapacitating agent with the active ingredient Oleoresin Capsicum (OC) - an oily concentrated extract from pepper plants of the genus Capsicum with potential to cause neurogenic inflammation and a catecholamine surge caused by the capsaicinoid. To our knowledge, only orally ingested Capsaicin has been reported to be associated with RCVS. Here we report a case directly linking the use of Pepper Spray with development of RCVS.

Case Presentation: A 24-year-old right-handed woman police officer with no known vascular risk factors presented to the emergency department for evaluation of thunderclap headaches which started several minutes after pepper spray to her face during work training. She denied taking any medications before her presentation. Neurological examination was unremarkable. Initial computed tomography (CT) of the brain showed no acute intracranial abnormality, however CT angiogram (CTA) of the head and neck showed multifocal mild arterial narrowing of bilateral middle cerebral arteries (MCA), bilateral posterior cerebral arteries (PCA) and left anterior cerebral artery (ACA) concerning for RCVS. She subsequently underwent conventional cerebral angiogram which confirmed these findings. Magnetic resonance imaging (MRI) of the brain showed no acute infarct. After initiation of nimodipine, the patient reported almost complete resolution of her headaches and was discharged home on oral nimodipine. Eight weeks later, she had a repeat CTA head and neck demonstrating almost complete resolution of multifocal narrowing of cerebral arteries, further supporting the diagnosis of RCVS.

Conclusions: This case highlights the typical clinical and imaging findings of RCVS and suggests an unusual trigger for the syndrome. Although the pathophysiology of this condition is still unclear, catecholamine storm following exposure to Pepper Spray may shed light on a novel mechanism contributing to development of RCVS. Routine use of Oleoresin Capsicum for law enforcement training or in other circumstances may be an independent risk factor for the development of RCVS.

288. New Onset Cervical Dystonia after Resolving Posterior Reversible Encephalopathy Syndrome (PRES): A Case Report and Literature Review

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Background: Clinical manifestations of PRES have been typically characterized as headache, altered mental status, visual disturbances, seizures, encephalopathy, and paralysis. PRES induced movement disorders have been reported as rare case reports.

Case Presentation: We present a case of cervical dystonia in a 32-year-old African American female with PRES secondary to multiple blood transfusions. The patient had history of severe vaginal bleed s/p D&C and multiple episodes of blood transfusion. The patient presented with RLE twitching, weakness, numbness, headache, N/V, dizziness, and visual disturbances. MRI brain revealed multiple areas of T2 hyperintensity associated with diffusion restriction bilateral posterior frontal and parietal cortex, posterior right occipital lobe suggesting areas of acute infarction consistent with atypical PRES. The clinical picture was consistent with PRES in the setting of hypervolemia/HTN related to transfusion versus immunologic reaction. Repeat MRI showed complete resolution of hyperintensities but there was small area of hemorrhage in the right internal capsule. Two weeks later she developed intermittent No-No head tremor, a 20% right side tilt and 20% turn in her neck. Patient was diagnosed with cervical dystonia due to hemorrhage in the internal capsule. Patient was advised to follow up at movement disorder clinic for cervical dystonia.

Discussion: There are scant reports of movement disorders associated with PRES and dystonia has been reported among these findings. It is important to have insight about possible permanent neurological deficits related to PRES. Here we present an unusual manifestation of PRES. These findings in cases preceded by PRES have been reported scantly. It would be beneficial to report more cases and enhance clinicians' insight into such rare sequela and outcomes of PRES.

289. A Case of Charles Bonnet Syndrome Following Anoxic Brain Injury

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Background: Charles Bonnet Syndrome (CBS) commonly presents as visual hallucinations in patients with vision loss. This has been seen in patients with visual acuity loss and visual field loss. There are many conditions that can result in vision loss and lead to CBS. CBS is seen when there is damage to the visual pathway by an acquired condition. It is not seen in conditions with non-acquired vision loss such as congenital blindness. Some common conditions where this phenomenon can occur are glaucoma, diabetic retinopathy, age-related macular degeneration, and cerebral infarctions.

Case: A healthy 38 year old male with no significant past medical history was playing soccer and suddenly lost consciousness. Cardiopulmonary resuscitation was performed until EMS arrived to the scene and determined that he was in ventricular fibrillation. There was return of spontaneous circulation after 28 minutes of advanced cardiac life support. CT of the brain showed diffuse white matter hypodensities in the frontal lobe, parietal lobe and basal ganglia which was reflective of hypoxic ischemic encephalopathy. After several days of care in the ICU, patient began to gradually awaken. He was found to have vision loss, and soon after it was discovered he was having visual hallucinations. When he would look towards his wife as she spoke, he would see another person standing next to her. As the weeks progressed, there were

also transient reports of visual hallucinations that involved seeing various colors. MRI of the brain performed at a later time did not show any new findings that were not previously known from the prior CT scan.

Discussion: This patient was experiencing visual hallucinations after acquired vision loss. This presentation is typical for CBS, even though there is no radiographical evidence of damage to the visual pathway to explain the vision loss. Due to the anoxic brain injury, there could have been damage that leads to disinhibition of the visual cortical areas resulting in these visual hallucinations. The patient received an ophthalmological evaluation, and was cleared of psychosis or delirium to rule out any other causes of the vision loss or the subsequent visual hallucinations.

290. Anatomical Substrate of QTc Prolongation in Acute Medullary Infarction

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Objective: To determine the spatial relationship between acute medullary infarction and QTc-prolongation.

Background: Ischemic stroke has been associated with QTc-prolongation [1, 2] which increases the risk of cardiac arrhythmia and sudden cardiac death. In particular, pathological arrhythmia and unexpected sudden cardiac death has been described after acute medullary infarction (AMI) [3-5]. Nevertheless, it is not well understood why only as subset of patients with AMI develop significant cardiac arrhythmia. To gain insight into this issue, we sought to determine the possible anatomical structures relating to QTc-prolongation in patients.

Methods: We retrospectively reviewed 1075 consecutive adult patients admitted for an acute ischemic stroke or a transient ischemic attack, who presented within 4.5 hours from the last known well time and had an admission ECG available. 726 patients had brain MRIs and among these, 13 (1.8 %) patients had an AMI and were included. For an unbiased lesion analyses, medullary infarcts were manually outlined on diffusion weighted MRI and manually co-registered with an anatomical atlas. Infarct lesions were then superimposed on each other as stratified by normal versus prolonged (men > 430, women > 450 ms) QTc to determine the area of greatest degree of congruence.

Results: 76.9 % of patients (10 out of 13, 9 men and 1 women) had a prolonged QTc (476.9 $\pm$ 43.3 for men, 515 ms for women). There was no significant difference in electrolyte levels and preexisting comorbidities between subjects with normal and prolonged QTc. Among patients with QTc-prolongation, the greatest degree of congruence of the infarct location was the dorsal vagal nucleus (DVN, 7 out of 10 patients). IRB approval is pending to expand our analyses to include more patients.

Conclusions: Our unbiased lesion segmentation approach identified the DVN a key anatomical substrate related to QTc-prolongation. Biological plausibility of our data and the presence of a causal link between the DVN and cardiac arrhythmia stems from the prior animal experimental data showing that selectively silencing the DVN via a pharmacogenetic approach caused QTc-prolongation in the rat [6]. Further studies with more patients and high-resolution, volumetric MRI are needed to confirm our findings.

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291. Small Fiber Neuropathy Mimicking Stroke, a Case of Adie Tonic Pupil of as a Consequence of Long Standing Small Fiber Neuropathy

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Background: Small-fiber polyneuropathy is the most common neuropathy.Presentation can vary from entirely somatic to entirely autonomic, but most patients have mixed symptoms.Skin biopsy is currently the best established test for objective confirmation of diagnosis. Here we present an unusual case of Adie tonic pupil of as a consequence of long standing Small fiber Neuropathy.

Case: This is a case of a 49 year old female with a history of Hodgkin lymphoma status post chemotherapy who was being followed up by neurology in clinic for bilateral lower extremity pain and numbness since last 5 years. After ruling out nutritional and toxic causes of neuropathy including Vitamin B12, B6, Niacin were checked and levels were within normal limits. Patient underwent a skin biopsy which came out positive for Small Fiber neuropathy and was being treated with Cymbalta and Amitriptyline. In March 2019, patient presented to the emergency room with Anisocoria with right pupillary dilation and headache. Right pupil was 5mm non reactive while left was 2mm and reactive. Patient was worked up for any aneurysm and cerebrovascular disease and all the workup including MRI brain and MRA head and neck were negative for cerebrovascular accident or aneurysm. Pt was discharged with follow up with ophthalmology with a working diagnosis of Adie Tonic pupil. Pt also followed up with ophthalmology where a dilute pilocarpine test was done but was inconclusive as patient was already on oral pilocarpine for dry mouth and suspected Sjogren syndrome. Patient's anisocoria improved with time.

Discussion: The case demonstrates an extremely rare form of small fiber neuropathy in a 49 years old female presented with somatic SFN who developed Adie's tonic pupil.SFN refers to widespread preferential damage to the small-diameter somatic and autonomic unmyelinated C-fibers and/or thinly myelinated A-delta fibers.Traditional descriptions of SFN emphasize spontaneous and stimulus-evoked distal skin pain and sensory loss, but deep aching, fatigue, postexertional malaise, and neuropathic itch are also common. Less commonly, it was reported that patients with SFN presented with autonomic disturbance like postural orthostatic tachycardia syndrome, gastrointestinal complaints, and

sweating complaints reflecting damage to postganglionic unmyelinated autonomic small fibers. This patient's findings highlight the importance of the understanding of small fiber neuropathy spectrum of semiology, and the need for more research on the presentation and treatment of autonomic SFN.

292. A Case of Venous Loop Causing Glossopharyngeal Neuralgia

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Background: Glossopharyngeal neuralgia (GPN) is a very sporadic condition related to hyperactivity of the glossopharyngeal nerve. Glossopharyngeal neuralgia is a rare condition, commonly misdiagnosed as trigeminal neuralgia The pain affects the sensory areas corresponding to the glossopharyngeal neuralgia with a branch of sensory vagus nerves. GPN consists of spasmodic, momentary, and severe sharp pain in the posterior area of the throat, tonsillar fossa, base of the tongue, ear canal, and areas inferior to the angle of the mandible. Idiopathic glossopharyngeal neuralgia may be due to compression of the glossopharyngeal nerve by adjacent vessels, while secondary glossopharyngeal neuralgia is associated with identifiable lesions affecting the glossopharyngeal nerve at different levels of its neuroanatomic pathway. This article describes a rare case of GPN due to compression by a venous loop.

Case: Patient is a 29 year old male presented to neurology clinic 12/2018 describing an episode of URTI in 2017 after which he developed severe dull pain in the right throat, posterior tongue, right face, and right ear in addition to ringing and fullness of right ear.He received multiple antibiotics and steroids. He underwent barium swallow and CT neck soft tissues which were negative. He underwent right tonsillectomy and posterior tongue resection in 4/2018 without improvement. He was given diagnosis of postinfectious trigeminal neuralgia. On presentation he had hyperestheisa on right face. He was given a working diagnoses of trigeminal neuralgia vs glossopharyngeal neuralgia vs atypical facial pain syndrome. MRI brain and CTA head and neck ordered and showed a venous structure in the region of the right superior olivary fossette which is the entry site for the glossopharyngeal nerve. Patient is stable with symptomatic treatment. He's not aiming for further interventions.

Discussion: Idiopathic glossopharyngeal neuralgia may be due to compression of the glossopharyngeal nerve by adjacent vessels, while secondary glossopharyngeal neuralgia is associated with identifiable lesions affecting the glossopharyngeal nerve at different levels of its neuroanatomic pathway including neoplasms, vascular malformations, demyelinating diseases (multiple sclerosis), infection, trauma, Chiari malformation, Eagle's syndrome, and choroid plexus overgrowth. A review of the literature reveals that the number of reported cases of vascular compression is very limited.To our knowledge, this is the first report of the association between GPN and This case highlights the importance of being aware of GPN when patients present with unusual facial pain. Vascular imaging to exclude such a diagnosis is recommended.

293. Difference in Inpatient Clinical Outcomes of Acute Ischemic Stroke Patients Based on Brain MRI Utilization

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Purpose: Inpatient MRI is often used in the radiological workup of acute ischemic stroke (AIS) due to its strong performance profile. Use of inpatient brain MRI in AIS patients is highly institution-dependent and has been associated with increased length and cost of hospital stay. We examined whether inpatient brain MRI in AIS patients is associated with improved clinical outcomes to justify its resource requirements.

Methods: The National Inpatient Sample database was queried retrospectively to find 94,003 patients who were admitted for AIS and then received inpatient brain MRI between 2012 and 2014 in the United States. Multivariate regression analysis was performed with respect to a control group to assess the impact of brain MRI on the rates of inpatient mortality and complications, as well as the length and cost of hospital stay.

Results: Unadjusted mortality rate was lower in the MRI group at 1.67% compared to 3.09% in the control group. On multivariate regression analysis, undergoing inpatient brain MRI was independently associated with lower mortality (adjusted OR 0.60, 95% CI 0.53-0.68, $P<0.001$). Brain MRI was also independently associated with a significantly lower incidence of gastrostomy (2.28% vs. 2.89%, adjusted OR 0.82, 95% CI 0.73-0.93, $P<0.001$) and mechanical ventilation (1.97% vs. 2.82%, adjusted OR 0.68, 95% CI 0.60-0.77, $P<0.001$). No significant difference in the incidence of intracranial hemorrhage ($P=0.490$) and non-home discharge ($P=0.140$) was observed between two groups. Brain MRI was independently associated with approximately 7% (7 hours) and 11% ($1,150) increase in the total length ($P<0.001$) and cost ($P<0.001$) of hospital stay, respectively.

Conclusion: Inpatient brain MRI in AIS patients is associated with substantially decreased rates of inpatient mortality and complications, at the expense of marginally increased length and cost of hospitalization.

294. Association between Baseline Cognitive Function and Functional Outcome Change after Ischemic Stroke

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Background: Ischemic stroke can cause impairment of cognitive and daily living function. There have been many previous studies regarding the correlation between cognitive function and functional outcome. However, few studies studied the effect of baseline cognitive function on future functional recovery. Furthermore, there are no studies have studied the association according to the severity of stroke.

Objective: The aim of this study was to investigate the relationship between baseline cognitive function and

functional outcome change after ischemic stroke according to the severity of stroke.

Methods: We enrolled the patients from January 2017 to April 2019, who have been hospitalized under the diagnosis of ischemic stroke at Kangwon National University Hospital, South Korea. Of the total 1064 patients, we excluded the subjects without functional outcome at 1 year after the onset, or the results of baseline cognitive function, or with other systemic diseases that could affect the outcome. Finally, 229 subjects were analyzed.According to the severity of the stroke, subgroups were divided into minor (NIHSS 0 to4, N=164), moderate (NIHSS 5 to 8, N=46), and severe (NIHSS 9 or more, N=19). Mini-MentalStatusExamination (MMSE) was scored to evaluate the baseline cognitive function. Modified Rankin Scale(mRS) was used to assess functional outcome at the time of discharge and after 1 year. The association between baseline MMSE and change of mRS was analyzed with multivariable linear regression analysis after controlling age, sex, presence of HTN, DM, coronary heart disease, and NIHSS.

Results: Of the 229 subjects, the mean age of the patient was 73.9, and 48% was female. In minor stroke groups, higher baseline MMSE was associated with a greater decreaseof mRS (p= 0.029). For patients with an MMSE score higher than the average, the distribution of mRS score 0 or 1 increased from 76% to 84% after 1 year, but the group below the average, the distribution decreased from 79% to 71%. In moderate or severe groups, we could not find any significant associations.

Conclusion: After ischemic stroke, higher baseline cognitive functionwas associatedwith a greater decrease in mRS at one year inthe minor stroke group, but not in the moderate or severe group. The baseline cognitive function could affect the recovery of functional outcome and this association could be different according to the severity of stroke.

295. Limb Shaking Ischemia and Vertebral Artery Stenosis

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Repetitive involuntary movements are a well described clinical manifestation, usually associated with carotid occlusive disease. We describe a novel case of a woman with recurrent brief involuntary spasms due to vertebral artery occlusive disease resulting in left cerebellar ischemia. An octogenarian with a medical history of thyroid cancer, breast cancer, alcohol abuse, dementia, and hypothyroidism was transferred to our institution to further evaluate new onset involuntary left arm movements. Recurrent brief episodes of involuntary left arm movements had begun a few days prior to admission and were associated with dizziness but no residual neurologic deficits. A live video recorded by a family member demonstrated stereotypic movements involving her left elbow and wrist, with non-rhythmic dystonic contractions of the left hand and extension of the left 2nd to 5th digits at the metacarophalangeal joints. Long term video EEG did not show any focal epileptiform abnormalities. MR Brain Imaging revealed an acute infarct of the left cerebellum in the posterior inferior cerebellar artery (PICA) territory; MR angiogram revealed moderate stenosis at the origin of the left cervical vertebral artery, lack of flow related signal throughout the left cervical vertebral artery, and just a faint flow related signal within the distal intracranial left vertebral artery. Positive symptoms such as new involuntary movements are often associated with suspicion for seizure or movement disorder rather than stroke. Multiple reports of Limb Shaking TIA or ischemia can be found associated with hemodynamic stenosis involving the carotid or middle cerebral artery (MCA). Here, we present a classic presentation of limb shaking ischemia due to hemodynamic stenosis within the vertebral artery. It is unclear what mechanism provoked the involuntary movements, especially since lack of focal epileptiform activity on EEG argues against an epileptic phenomenon.

296. A Case of an Embolic Stroke Following Mesenteric Arteriogram

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Introduction: Embolic stroke most often occurs suddenly where deficits indicating focal loss of brain function are maximal at onset. Embolic stroke is a well-known complication of coronary catheterization, aortography and cerebral angiogram, but to the best of our knowledge, there is no reported case of a stroke following abdominal/mesenteric arteriogram.

Case Report: 69-year-old right handed woman with hypertension, diabetes, hyperlipidemia and peripheral arterial disease was admitted to the hospital with nausea and vomiting with suspected mesenteric ischemia. Abdominal arteriogram showed patent celiac trunk and superior mesenteric artery but showed chronically occluded inferior mesenteric artery. A SIM-2 catheter was used during the procedure, which was formed in the aortic arch against aortic valve and then pulled back down for selective catheterization. Shortly following the procedure, she was noted to have left facial droop, left hemiparesis and left hemihypoesthesia (NIHSS 7). CT brain was unrevealing of an acute intracranial pathology. CTA head and neck did not show any significant craniocervical large vessel severe stenosis or occlusion but showed severe calcified and noncalcified atherosclerotic disease in the aortic arch and proximal descending aorta. She was treated with IV tissue plasminogen activator (tPA). MRI brain subsequently showed multiple embolic-looking acute infarcts in multiple vascular distributions involving both anterior and posterior circulations as well as involving both cerebral and cerebellar hemispheres. Cardiac monitoring during hospitalization did not reveal any evidence of atrial fibrillation. Transesophageal echocardiogram was planned but not performed due to patient's refusal.

Discussion: Embolic stroke in the setting of aortic arch atheroma represent a subgroup of cryptogenic stroke or an embolic stroke from undetermined source. Periprocedural stroke described here likely represent an embolism from aortic arch atheroma being the most likely mechanism of stroke in our patient. Periprocedural stroke with respect to abdominal/mesenteric angiogram is rare, however noninvasive

imaging like CTA chest to profile aortic arch in an order to rule out severe aortic arch atheroma as well as to help guide proper catheter technique during the procedure is proposed.

297. Atypical Leukoencephalopathic Changes with Chronic Methamphetamine Abuse

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Objective: Drugs such as cocaine, heroin and methamphetamine are known to cause toxic leucoencephalopathy. Different patterns have been described in relation to different toxic metabolic agents. The CNS effects of Methamphetamine abuse include ischemia and stroke. The imaging findings involves increase signal intensity on T2/FLAIR in white matter, reduced cortical gray matter, changes in striatal volume. We report a case of methamphetamine abuse with involvement of thalami, brainstem and cerebellar white matter.

Case: A 43 year old female with history of HTN and methamphetamine use (daily for the past 4 years) presents with AMS and blurry vision in the setting of elevated blood pressure in the 230s/150s mmHg. She was admitted for hypertensive urgency. On physical examination she was alert and oriented x4 with slurred speech, but intact language. She had disconjugate gaze but no nystagmus, otherwise cranial nerves intact. She had dysmetria of left extremities as well as ataxic gait. UDS was positive for methamphetamine use and labs were significant for leukocytosis (15.51/uL), hypokalemia (2.4 mmol/L), elevated creatinine (1.09mg/dl) troponin (0.05 ng/ml) and TSH (7.59 mIU/L). CT head showed diffuse cerebral edema. MRI brain without contrast showed symmetric hyperintense T2/FLAIR signal throughout the thalami, brainstem and cerebellarwhite matter with patchy signal abnormality in the frontoparietal lobes and a punctate acute/subacute infarct in the right lentiform nucleus. In comparison to MRI brain with without contrast done a month ago, white matter changes were stable. The tiny punctate infarct was pattern, however the pattern and distribution are suggestive of hypertensive encephalopathy however these additional findings are suggestive of drug induced Leukoencephalopathy. CT angiogram of the head and neck showed 60% stenosis of the left vertebral artery but no vasospasm, no carotid stenosis. Transthoracic Echo with No PFO and normal EF. following blood pressure control, patients mental status reverted to baseline, however the exam continues to reveal slurred speech, disconjugate gaze, Ballistic movements in LUE & LLE.

Conclusions: This case represents an atypical pattern of leukoencephalopathy in the setting of chronic methamphetamine abuse. In addition to PRES which is reversible, one must consider toxic causes such as methamphetamine upon seeing such findings on imaging.

298. Excessive Caffeine Intake from Energy Supplements as a Cause of Ischemic Stroke in Young Patients

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Introduction: Stimulants such as amphetamine and cocaine are well known causes of ischemic stroke. Caffeine, an adenosine A2 receptor antagonist, is the most commonly used beverage worldwide. It has been reported that caffeine intake of more than 250mg can decrease the Blood flow by 30%. A meta-analysis in 2012 reported the preventive effect of coffee (4 cups or more) on reducing stroke. However, a more recent study (Yang et al 2019) confirmed the vascular effect of reduced CBF due to caffeine using BOLD fMRI. We report a case of ischemic stroke associated with excessive caffeine intake alone.

Case Report: A 36 male history of drug abuse and untreated HTN who initially presented with right sided weakness and slurred speech. In the emergency department, his NIHSS was 11 and his CT head was negative for hemorrhage, so he subsequently received IV tPA. History revealed that patient had abstained from drugs (cocaine, methamphetamine, Adderall) for the past 6 months and his UDS was negative on arrival. Instead, he had been using increasing amounts of caffeine. On the day prior to presentation, the patient had ingested 4-5 "Monster Energy" (640 mg caffeine) drinks and 8 "Stackers" B-12/caffeine capsules (unclear caffeine amount). CTA head and neck did not show any atherosclerotic disease or evidence of vasospasm. MRI brain showed an acute infarct in the left lentiform nucleus and left caudate. In the next 24-hrs, his symptoms resolved with NIHSS 0. Stroke work up revealed HgbA1C 5.5, LDL 155, and negative hypercoagulability studies. TEE demonstrated a small PFO with R to L atrial shunt; however there was no atrial septal aneurysm and his ROPE score was 5.

Conclusion: This is the only reported case of Ischemic stroke due to excessive caffeine intake alone (at least 640 mg daily). In addition to decreasing blood flow by perhaps inducing vasoconstriction, caffeine possibly contributed to elevated BP as well in our patient.

299. Cerebral Venous Sinus Thromboses (CVST) with Stroke Symptoms in a Patient with Controlled Ulcerative Colitis

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Introduction: Ulcerative Colitis (UC) is a disease of the colorectal mucosa marked by severe inflammation presenting as severe abdominal pain, bloody diarrhea, nausea/vomiting, loss of appetite and weight loss. Patients are at increased risk of hypercoagulability due to multitude of reasons including severe significant inflammatory response as well as imbalance of coagulant-anticoagulant proteins that could favor increased coagulability. This increases risk of cerebral venous thrombosis which occurs with an estimated annual incidence rate of 0.5 to 7.5% (PMCID: PMC5359939). On literature Review, we found multiple cases of UC associated with CVST but all the cases were linked with UC flare. Here we report a case of CVST that suggests the risk of thrombosis may persists despite the Inflammatory bowel disease (IBD) being under control clinically.

Case Report: A 35-year-old right-handed man with history of well-controlled UC on mesalamine presents with two-day history of worsening headaches and intermittent right arm numbness/weakness and intermittent aphasia on the day of presentation. Neurological exam was remarkable for right

arm weakness and numbness as well as mild to moderate expressive aphasia. CT brain and MRI brain showed evolving venous infarct in the left inferior frontal lobe. CT Venogram of head showed diffuse superficial cerebral venous sinus thrombosis involving superior sagittal sinus (SSS), left transverse and left sigmoid sinuses. Video-EEG showed focal slowing in the left fronto-temporal region without any epileptiform discharges. Cerebral angiogram confirmed cerebral venous sinus thrombosis as seen on CTV. Hypercoagulable workup, infectious workup & inflammatory markers were unrevealing. Urine drug screen was negative. Pt reported be in remission as last flare up of UC was 9 months ago. Patient was discharged on therapeutic anticoagulation with Lovenoxbridging to warfarin.

Conclusion: Inflammatory bowel disease (Crohn's disease and Ulcerative colitis) regardless of the disease state, can predispose patients to higher risk of thrombosis associated with increase in morbidity and mortality. CSVT should be considered as a differential diagnosis in patients with IBD regardless of disease activity as this can expedite management and treatment. Our patients stroke like symptoms & headache improved after starting therapeutic anticoagulation. Therefore, in addition to management of Ulcerative colitis, patients should be educated about possibility of stroke-like symptoms and prophylactic therapy with Anticoagulation should be considered.

300. Bilateral Acute Ischemic Stroke: Rare Case of Bilateral Internal Carotid Artery Hypoplasia

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Introduction: Internal carotid artery (ICA) hypoplasia is a rare anomalous embryonic process in 26th week of development involving the third pharyngeal arch artery. A bilateral hypoplastic ICA is even rarer with few cases reported to date. We present a case of bilateral hypoplasia of ICA presenting as bilateral acute infarcts in the frontoparietal regions.

Case: A 39-year-old, right-handed woman presented to the emergency department with a sudden acute onset of headache, delirium with irritability and right-sided leg weakness that resulted in patient having a fall. She had no prior history of trauma or connective tissue disease. CT head demonstrated hypo densities in left frontoparietal and right parietal lobes. MRI brain without contrast exhibited acute multifocal infarcts affecting both hemispheres predominantly in cortex and juxta-cortical white matter. CTA head and neck revealed significant narrowing of bilateral ICA starting 1cm after the bifurcation and extends intracranially with almost occlusion of cavernous internal carotids. Digital subtraction angiography was consistent with diminutive bilateral ICA as it branches of Common Carotid Artery along with areas of stenosis in the right Vertebral artery. Trans-thoracic Echo did not show any abnormality. Metabolic, inflammatory markers and hypercoagulable panel were normal. Vasculitis was ruled out. Patient was started on aspirin and low-dose statin for secondary prevention. Permissive hypertension was advised. Clinical improvement in neurological status was noticed over time.

Conclusion: Bilateral hypoplasia of the internal carotid arteries can present with bilateral acute ischemic strokes. Prompt diagnosis and management is prudent in prevention however data is lacking on the usefulness of screening and primary prevention due to rarity of the anomaly and variety of presentations.

301. Impact of COVID-19-Related Physical Distancing on Mental and Physical Health of People with Recent Stroke

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Background: Physical distancing, while reducing the spread of COVID-19, may lead to negative consequences such as social isolation, impeded access to care, reduced exercise, and depression.

Objective: To understand the effects of physical distancing on physical and mental health of recent ischemic and hemorrhagic stroke patients.

Methods: We conducted a qualitative study in spring 2020 of patients discharged from BIDMC with recent ischemic or hemorrhagic stroke before the COVID pandemic. Purposeful screening ensured adequate representation by sex, race/ethnicity and hospital discharge disposition. We completed a semi-structured interview by phone with the patient, or if unable, a proxy. Interviews were recorded, transcribed, and analyzed through rapid qualitative analysis (Sperber et al., *Qual Manag Health Care*, 2019) to identify themes. Saturation of themes was achieved, defined by no new themes from 3 consecutive interviews.

Results: From 17 participants (10 patients, 7 proxies), five themes emerged: 1) altered social dynamics, 2) decreased ability to do things they enjoy, 3) negative mental health effects, 4) decreased access to healthcare, and 5) positive adaptations and coping strategies. Patients interviewed directly were less disabled (n=10, median modified Rankin Scale (mRS) 1), less likely to report negative health impacts, and more likely to describe adaptations and coping strategies, compared to those interviewed by proxy (n=7, median mRS 4) and especially participants in facilities at the time of interview. While social interactions decreased overall, in some cases participants spent more time with household members. Participants were less able to engage in normal activities, often leading to decreased physical activity. Particularly for participants in facilities, mental health effects included worsened depression, loneliness, and lack of motivation. Appointments with physicians and physical or speech therapy were often cancelled. Personal adaptations including use of telemedicine, phone calls, video conferencing, and physically distanced visits with family or friends were protective for mental health. Examples of individual coping strategies that also appeared protective included spirituality, continued exercise, and optimism.

Conclusion: Distancing can lead to isolation and affect the physical and mental health of recent stroke patients. Patients in facilities seem particularly at risk. Protective factors include technology use and frequent contact with friends and family. Our findings may help equip clinicians to identify patients at risk of isolation and depression during the COVID pandemic and offer hypotheses to identify at-risk groups for social isolation after the pandemic ends.

302. Spontaneous Vertebrobasilar Artery Dissection in a Patient with Ankylosing Spondylitis: An Association or a Co-Incidence?

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Background: Cervicocerebral arterial dissection is one of the common causes of ischemic stroke in young and middle-aged adults. Preceding history of mechanical triggering events like trauma is associated in up to 40% of such cases whereas spontaneous carotid and vertebral artery dissections account for about 10-25%. Connective tissue and vascular disorders commonly associated with spontaneous cervicocerebral artery dissection include fibromuscular dysplasia, Ehler-Danlos syndrome type IV and Marfan syndrome. Ankylosing spondylitis (AS) is associated with abdominal, thoracic, and coronary artery aneurysms. However, the association between AS and intracranial arterial dissection remains unknown.

Case Presentation: A 56-year-old right-handed man with medical history of well-controlled hypertension and ankylosing spondylitis presented to the emergency department for sudden onset neck pain and occipital headache without any associated focal neurological symptoms. There had been no recent trauma or other triggering events. Neurological exam was unremarkable. Initial computed tomography (CT) head showed no acute abnormalities, CT angiogram head and neck and subsequent conventional angiogram revealed intradural left vertebral artery dissection with complete occlusion of the intracranial (V4) segment with extension into the proximal to mid basilar artery. Magnetic Resonance Imaging (MRI) Brain demonstrated acute infarction in the left ventrolateral pons. Laboratory workup including urine drug screen and genetic testing to evaluate for connective disorders was unremarkable. His vital signs including blood pressure measurements on admission and throughout hospitalization were unremarkable. He had an uneventful hospital course and was discharged home on antiplatelet therapy.

Conclusion: Spontaneous intracranial/intradural vertebrobasilar artery dissection is rare and is usually associated with severe hypertension, such as occurs in cocaine use. AS is associated with cardiovascular complications such as aortic dissection and aneurysms, which raises suspicion for its possible association with arterial connective tissue integrity, predisposing to dissection. Here we present a case of ankylosing spondylitis associated with spontaneous vertebrobasilar artery dissection. Further study to determine AS's clinical relevance in cervicocerebral artery dissection is proposed.

303. Munchausen Syndrome by Tissue Plasminogen Activator (tPA): Patients Seeking Thrombolytic Administration

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Background: Intravenous tissue plasminogen activator (tPA) is sometimes administered for factitious stroke symptoms, but rarely reported. Here, we present a series of cases of Munchausen syndrome by tPA, prevalence in our stroke center, and highlight one illustrative case.

Methods: Cases were identified by review of departmental logs of acute stroke evaluations and discussion with physicians administering tPA. Through discussion and chart review, Munchausen syndrome by tPA was confirmed if the patient exhibited factitious symptoms to assume the role of the sick patient, the patient desired and received tPA, and no alternative diagnosis or secondary gain better accounted for the presentation.

Results: Of 335 cases with tPA administration over 29 months, 10 were confirmed as Munchausen syndrome by tPA, reflecting a 3.0% prevalence. Nine of 10 patients had symptom duration less than 70 minutes prior to evaluation, 7 had left-sided symptoms, 7 had multiple prior presentations, 8 reported prior TIAs or strokes, and 8 of 9 who received a brain MRI had no prior infarct. All patient exams were improved or normal by discharge.

Conclusion: Munchausen syndrome by tPA is an underappreciated phenomenon encountered in evaluating patients with acute stroke symptoms. Administering tPA in Munchausen syndrome poses an ethical dilemma as standard of care favors rapid tPA administration but administration can cause harm, adds financial burden to the healthcare system, and does not break the cycle of patients continuing to seek inappropriate healthcare. Rapid review of electronically-available outside records may help discern patients seeking tPA for factitious stroke symptoms.

304. Comparison of Functional Outcome after Mechanical Thrombectomy between Diabetic and Non-Diabetic Patients

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Objective: To compare the functional outcome after mechanical thrombectomy (MT) for large vessel occlusion (LVO) between patients with and without a history of diabetes mellitus (DM).

Background: DM causes pathological changes in large and small blood vessels, making it stiff and friable. Reperfusion after MT in diabetic patients have a risk of symptomatic bleed and poor functional outcome.

Method: A retrospective analysis was done at the University of Louisville hospital among all the cases who underwent MT between 2014-2018. 35 diabetic patients were identified: diabetic group (DG). A control of 35 non-diabetic patients; non-diabetic group (NDG), were randomly selected.

Demographics, history of hypertension, NIHSS on admission, last known normal (LKN) to groin time, TICI score, hemispheric side of stroke and mRS on discharge were reviewed. TICI score ≥2b was considered successful revascularization. Good outcome was mRS 0-2. Descriptive analysis, independent T-test and Spearman correlation were used as statistical tools.

Results: Total cases were 70. Mean age of DG vs NDG was 67.7 (SD 11.5) years old (yo) vs 55.5 (SD 13.4) yo. Total hypertensive cases in DG vs NDG were 33 vs 25 *(p 0.01)*. Median NIHSS on admission for DG vs NDG was 18 (IQR 15-20) vs 15 (IQR 11.5-21.75) (p 0.47). Median time for LKN to groin for DM vs NDG was 351.5 (IQR 229-517.7) vs 329.5 (IQR 228.5-725) (p 0.68). Successful revascularization for DM vs NDM was 35 (92%) vs 32 (84%) (p 0.29). Median Mars at discharge for DG v's NDG was 4 (IQR 4-6) vs 4 (IQR 1-4) *(p 0.00)*. Good outcome for DG vs NDG was 4 (10.5%) vs 13 (34.2%) *(p 0.01)*. Total deaths in DG vs NDG were 12 and 4 *(p 0.02)*. Increased age was not associated with increased mRS in DG (rho 0.11, p 0.55) and NDG (rho -0.55, p 0.75). Increased NIHSS was associated with increased mRS in DG (rho 0.42, *p 0.01*). Median mRS at discharge in right sided (n 17) vs left sided (n 18) stroke among DG was 4 (IQR 3-5) vs 4.5 (IQR 4-6) (p 0.14).

Conclusion: This single center study suggested poor functional outcome at discharge of diabetic patients compared to non-diabetic patients after MT for LVO. Poor functional outcome among diabetic patients was associated with increased initial NIHSS but was not associated with increased age and hemispheric side of stroke.

305. Stroke Epidemiology in Adults with HIV Infection in Zambia

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Objective: Describe epidemiology of stroke among Zambian patients with and without HIV infection.

Background: Approximately 35.3 million people worldwide are living with HIV/AIDS. More than 26 million of those are in sub-Saharan Africa, and there are over 2 million new infections every year. In Zambia, 12% of adults are living with HIV/AIDS. HIV is increasingly being recognized as an independent risk factor for stroke. Understanding the epidemiology of stroke in HIV infection may lead to better stroke prevention and treatment in these patients.

Methods: We completed a prospective cohort study of consecutive stroke patients admitted to the University Teaching Hospital in Lusaka, Zambia between October 2018 - April 2019. Standardized data collection instruments were used to collect demographic, clinical, laboratory and imaging results. Strokes were classified as ischemic (IS) or hemorrhagic (HS) based on CT appearance. Descriptive statistics were calculated for patients with and without HIV infection and compared using t-tests for continuous variables and chi-square analyses for categorical variables.

Results: A total of 268 stroke patients were enrolled with a confirmed HIV status. Average age was 48 (SD 14) years for HIV-infected (HIV+) versus 62 (SD 18) years for HIV-uninfected (HIV-) (p<0.001). Neither sex (65% female), stroke subtype (57% IS in both groups), in-hospital mortality, or ninety-day post-discharge mortality varied by HIV status. Among those with ICH, HIV+ patients had higher ICH scores compared to HIV- patients (28% vs 11% score 3 or 4, p=0.030). HIV+ patients were less likely to have hypertension (66% vs 88%, p=0.04) and be taking medications for diabetes (0% vs 9%, p=0.046). DVT (4% vs 1%, p=0.03) and fever (22% vs 15%, p<0.001) were more common during hospitalization amongst HIV+ patients.

Conclusion: This Zambian HIV+ stroke cohort is notable for being significantly younger with less hypertension and diabetes but higher ICH scores than their HIV- counterparts. HIV+ patients were more likely to have longer hospitalizations, DVT, and hospital course complicated by fevers. Our results reflect the significant role of HIV infection in the growing burden of stroke in Zambia, which needs to be addressed for both improved treatment and primary stroke prevention.

306. Human Plasma Proteomics for Biomarker Discovery for Ischemic Stroke and Transient Ischemic Attack

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Background: Previous studies have shown that the proteomic analysis of plasma proteins is a reliable tool to identify blood-based biomarkers in acute stroke. However, transient ischemic attack (TIA) can often be difficult to distinguish from stroke mimics especially in the emergent setting. Blood-based biomarkers to distinguish these entities could be immensely useful.

Objective: We hypothesized that mass spectrometry-based proteomic profiling of plasma collected from patients with acute ischemic stroke, TIA and stroke mimics is a feasible strategy to differentiate these diagnostic groups.

Design/Methods: Blood was drawn acutely upon patient presentation to the emergency room and plasma was stored at -80 °C. 29 age and sex-matched cases (7 TIA, 10 ischemic stroke and 12 stroke mimics) were selected. Top-14 highly abundant (e.g. albumin, globulins) proteins were depleted. Pre- and post-depletion BCA and Coomassie gels were run to confirm adequate and equal depletion. Proteins were digested with Lys-C and trypsin and processed for label-free quantitation mass spectrometry (LFQ-MS). Data were analyzed by differential expression and principal component analysis (PCA).

Results: LFQ-MS of plasma samples identified 400 proteins of which 279 had <50% missing values and were included for analysis. 51 proteins were differentially expressed across the three groups and PCA identified 3 PCs that explained 47.5% of the variance in the data (PC1:23.3 % PC2:14.9% PC3: 9.3%). PC1 differentiated TIA from mimics while PC2 differentiated stroke from TIAs and

mimics. Higher levels of fibrinogen and complement activation differentiated TIA from mimics while higher levels of acute-phase reactants (CRP, SAA1) differentiated TIA from ischemic stroke.

Conclusions: We establish the feasibility of proteomic analysis of plasma as an approach to identify novel stroke and TIA biomarkers. Ongoing comprehensive validation studies of these plasma biomarkers will allow us to develop diagnostic panels to differentiate TIA from Stroke mimics in the emergency room setting.

307. Diffusion Tensor Imaging Profiles of Thalamic Nuclei and Thalamocortical Pathways and Their Role in Naming after Stroke

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Introduction: The dorsal medial and ventral anterior nuclei complex (DMVAC) and the pulvinar lateral posterior nuclei complex (PLC) are thought to be engaged in language-related processes. That thalamic lesions can lead to language impairments has been known for a long time. However, most of the previous stroke literature utilized lesion centric approaches (e.g., lesion-symptom mapping) to study the role of the thalamus in the aphasia. We hypothesized that normal-appearing dorsomedial and ventral anterior nuclei (DMVAC) and pulvinar lateral posterior nuclei complexes (PLC) of the thalamus and their projections to the left-sided cortical areas would show secondary effects of the strokes, and their microstructural integrity would be closely related to language-related functions.

Methods: Thirty patients with varying degrees of language impairment after left hemispheric stroke sparing the thalamus underwent concurrent Boston Naming Test (BNT) and diffusion tensor imaging (DTI). The tissue integrity of DMVAC, PLC, and their cortical projections were quantified with DTI. The right-left asymmetry profiles of these structures, as well as laterality index (LI) of DTI metrics assessing left hemispheric dominance over the right, were evaluated. The association of their microstructural integrity with BNT scores was investigated with partial correlation analyses adjusted for age, education, lesion load, and time since stroke. The results were corrected for multiple comparisons.

Results: Both DMVAC and PLC show lower mean diffusivity (MD) on the right side compared to the left side (p=0.004 and p=0.0006, respectively). LI of PLC MD was significantly associated with BNT (r=-0.59, p=0.0006). The right PLC cortical projections had higher tract FA compared to the left (p=0.0002). LI of PLC cortical projections FA was correlated with better outcome (r=0.63, p=0.0002).

Conclusion: Normal-appearing thalamic nuclei and thalamocortical pathways show rightward lateralization of the microstructural integrity after a left hemispheric stroke, and this pattern is associated with poorer naming performance. To the best of our knowledge, our study is the first study in the post-stroke aphasia literature showing the secondary degeneration in the relevant thalamic nuclei and thalamocortical connections in relation to language-related processes.

308. Correction of the Edema Effect on the Myelin Content Estimation Using Macromolecular Proton Fraction (MPF) Mapping in a Rat Ischemic Stroke Model

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Introduction: Fast macromolecular proton fraction (MPF) mapping is a recently developed quantitative MRI method, which demonstrated high sensitivity to myelin content changes in the brain, particularly in a rat model of ischemic stroke. However, edema in the ischemic lesion leads to an increased tissue water content causing overestimation of the extent of demyelination by MPF.

Purpose: The study aimed to histologically validate and compare two techniques for correction of MPF values in the presence of edema in a rat ischemic stroke model.

Methods: Local brain ischemia was induced in male Wistar rats (n=6) by transient occlusion of the middle cerebral artery (MCAO). MRI was performed before and at days 0, 1, 3, 5, 7, 14, 21, 31, 42 and 56 after surgery. Quantitative MPF and T2 maps were obtained using ClinScan 7T small-animal MRI scanner. Two approaches accounting for changes in tissue water content were used to correct the effect of edema on MPF: 1) calculation of a correction coefficient based on a volume increase in the ipsilateral hemisphere relative to the contralateral one; and 2) bivariate regression model with MPF and T_2 as predictors, which was demonstrated to improve correlation with myelin content in a previous study. Both techniques were compared to histological staining with luxol fast blue (LFB) and myelin basic protein (MBP), which were performed at days 7, 21 and 56.

Results: A significant decrease in MPF (maximal at day 1 - 39%) in the ischemic lesion relative to preoperative values was observed at all timepoints ($p<0.05$) for each correction technique. Demyelination in ischemic core was confirmed by LFB and MBP staining. Application of corrections reduced differences in MPF values between ipsilateral and contralateral hemispheres at days 1-7 by 3% ($p<0.05$) for volume-based correction and 10% ($p<0.05$) for T2-based correction. Subsequently, the differences increased by 3% ($p<0.05$) for volume-based correction (days 21-56). MPF showed better agreement with dynamics of MBP and LFB changes after applying corrections.

Conclusions: Correction of the edema effect improves accuracy of quantitative assessment of the brain demyelination in ischemic stroke. T2-based correction appears more sensitive to edema than volume-based correction.

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K-582. **Identifying patients with intracerebral hemorrhage who may forego intensive care unit admission: A novel risk score in the COVID-19 era***

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Background and Purpose: Patients with intracerebral hemorrhage (ICH) are commonly monitored in an intensive care unit (ICU), however, objective data guiding need for ICU admission and prediction of ICU needs are largely lacking. In the COVID era, judicious use of critical care resources is of particular importance as strained health care systems may face the challenge of triaging critically ill ICH patients in a resource-constraint environment. Our study aimed to develop a feasible risk score to identify ICH patients at low risk for critical care.

Methods: We retrospective analyzed data from 451 ICH patients between 2010 and 2018. The sample was randomly divided in a development and a validation cohort. Logistic regression was used to develop a risk score by weighting independent predictors of ICU needs based on strength of association.

Results: The rate of ICU interventions was 80.3%. Systolic blood pressure (SBP), Glasgow Coma Scale (GCS), intraventricular hemorrhage (IVH), and ICH volume were independent predictors of critical care. The following points were assigned for the risk score: SBP 160-190 mm Hg (1 point), SBP >190 mm Hg (3 points); GCS 8-13 (1 point), GCS <8 (3 points); ICH volume 16-40 cm^3 (1 point), ICH volume >40 cm^3 (2 points); presence of IVH (1 point). The score ranges from 0-9. In the validation group, the score achieved an AUC of 0.880 (95% CI 0.833-0.928). A score of <2 predicted absence of critical care needs with 65.2% sensitivity and 89.2% specificity, and a score of <3 predicted absence of critical care needs with 86.5% sensitivity and 79.8% specificity. Among patients with a score of 0 and no ICU needs during their ED stay, 93.6% remained without critical care needs.

Conclusion: Our score, combining information about SBP, GCS, IVH, and ICH volume, may be a useful predictor of ICU needs in ICH. Our score identifies ICH patients at low risk for critical care, and patients with a score <2 may be considered for management in a stroke unit without critical care capabilities.

K-583. Bedside Optical Monitoring of Microvascular Reperfusion during Endovascular Thrombectomy

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Introduction: Successful large vessel recanalization by endovascular thrombectomy does not always result in restoration of microvascular cerebral blood flow (CBF). We hypothesize that bedside optical monitoring of cerebral hemodynamic during thrombectomy will be more sensitive than angiography at detecting persistent microvascular hypoperfusion and correlate with final infarct volume and function outcome.

Methods: In this ongoing project, we deploy a bedside optical instrument consisting of a diffuse correlation spectroscopy (DCS) module and time-domain diffuse optical spectroscopy (DOS) module to monitor CBF and tissue oxygenation, respectively. Measurements are made with two source-detector separations in order to differentiate between scalp and cerebral flow. The rate of discordance between angiography and microvascular CBF will be calculated. mTICI score and microvascular reperfusion status will be correlated with final infarct volume and long-term functional outcome.

Results: 28 patients have been prospectively enrolled in this protocol thus far (target enrollment of 100). Patient demographics and stroke characteristics are outlined in **table 1**. To highlight different patterns of microvascular reperfusion, two cases of internal carotid artery occlusion are contrasted. In both cases, baseline imaging, treatment time, and angiographic recanalization was similarly favorable. In Patient 1, (**figure 1**) at the time of recanalization, a sudden and sustained increase in CBF and tissue oxygenation was observed. The final infarct was small, and the patient had an excellent long-term function outcome. In the contrasting case of Patient 2, (**figure 2**) pulsatility was diminished and recanalization did not result in a suddenly increase in CBF. Flow was labile after recanalization.

Conclusion: This ongoing prospective cohort will demonstrate the feasibility of using diffuse optics to monitor microvascular cerebral hemodynamics during mechanical thrombectomy, highlighting the difference between large vessel recanalization and microvascular reperfusion. Identifying patients with persistent microvascular hypoperfusion will provide future opportunities to individualized care based on each patient's physiology.

*For K-583 that Table 1, Figures 1 and 2 were not provided by the author.

K-586. Infarcts are associated with globally decreased cortical thickness in children with sickle cell disease

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Background: Infarcts occur in over a third of children with sickle cell disease. Infarcts have been associated with age-dependent total volume loss in children with sickle cell disease. Factors contributing to infarct risk, including anemia, hypoxia, may also impair brain growth and development. Children with sickle cell disease with and without infarcts have also been shown to have decreased cortical thickness compared to healthy controls. We hypothesized that among children with sickle cell disease, cortical thickness would be more decreased among those with infarcts than those without.

Methods: We utilized clinically acquired MRIs of 33 children with SCD. Each child had 1-14 MRIs available for a total of 134 scans. Freesurfer 5.3 calculated mean cortical

thickness for each hemisphere based on high resolution T1 images. Total mean cortical thickness was based on surface area-weighted average of the two hemispheres. If a child developed an infarct at any scan, all scans for that child were categorized as infarct. Mixed models compared cortical thickness between those with and without infarct, adjusting for age.

Results: Median age at scan was 11.8 years [9.1, 15.1]. Children without any infarcts (n=5) contributed 11 scans at median age of 11.0 [9.2, 14.8]; children with infarcts (n=28) patients contributed 123 scans at median age of 11.9. The median age for scan with first infarct noted was 7.6 [5.1, 11.9]. The mean cortical thickness among those without infarcts was 2.85 mm, and 2.59 mm in those with infarcts. Even after adjusting for age at scan, those with infarcts had thinner cortices (p=0.001).

Conclusion: Children with SCD who have infarcts have significantly thinner cortices compared to children with SCD without infarcts. Further investigation is needed to understand etiology and risk factors for decreased cortical thickness in SCD.

Dementia and Aging

525. Gamma Sensory Flicker for Patients with Prodromal Alzheimer's Disease: A Phase I Trial

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We and collaborators recently discovered that flickering lights and sound at gamma frequency (specifically 40 Hz) drive gamma frequency neural activity in multiple brain areas and reduce pathogenic proteins in mouse models of Alzheimer's disease (AD). These changes coincide with transformed microglia, the primary immune cells of the brain, altered immune signaling, and improved cognitive functions in mouse models of AD (Iaccarino*, Singer*, *et al. Nature*2016, Martorell*, Paulson*, *et al. Cell* 2019, Garza, *et al. J Neuroscience*2020). However the effects of gamma sensory flicker on AD pathology and immune signaling in humans are unknown. Thus, we performed a feasibility study in a small cohort of human subjects to test the safety of extended gamma flicker stimulation, tolerance to this stimulation, and adherence during home use in patients with prodromal AD. Ten amnestic MCI subjects with prodromal AD received 1-hour daily gamma flicker for 4 or 8 weeks at home with a delayed start design, such that half the subjects started 4 weeks of stimulation after a 4-week no stimulation period. We did not use a sham stimulus during the no stimulation period because of potential unintended effects, as we have observed in some animal studies. Primary outcomes were safety, tolerance, and adherence to gamma flicker stimulation. We also assessed exploratory biological outcomes including neural entrainment, amyloid beta and tau pathology, cerebral blood flow, immune signaling, and default mode network functional connectivity at baseline, after 4 weeks of no stimulation, 4 weeks of stimulation, and 8 weeks of stimulation. We found gamma sensory stimulation was safe with no adverse events related to treatment. Of 17 screened and enrolled subjects, 16 found the stimulation tolerable. On average adherence rates during the main phase of the study were 95.5% with all subjects having adherence rates greater than 89% during the study. While this study is not powered to draw conclusions about biological changes following gamma flicker, we found preliminary evidence that gamma flicker altered cytokines in the CSF,decreased EEG power in the gamma band,and strengthened functional connectivity between nodes in the default mode network. These findings suggest that gamma sensory flicker is safe, tolerable, and feasible to perform at home with promising indications of immune and network effects. Thus, further study of gamma stimulation in Alzheimer's disease is warranted.

526. Deep Proteomic Analysis of Alzheimer Disease Brain Identifies New Protein Co-Expression Modules Associated with Disease That are Not Observed at the RNA Level

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Our understanding of the biological pathways that are altered in Alzheimer's disease (AD) remains incomplete. We recently reported the results of a large multicenter study that analyzed approximately 3000 proteins across hundreds of brain tissues by mass spectrometry-based proteomics to better understand these changes. We identified multiple biological alterations in AD brain, some of which likely reflect upstream disease pathophysiology. Here, we extend our analysis to include a significantly greater number of proteins (~9000) measured across >500 dorsolateral prefrontal cortex tissues from multiple centers using newer mass spectrometry-based quantitative approaches. The greater depth of proteome coverage allows us to identify new protein co-expression modules that are correlated to AD phenotypes. Similar to modules we have previously identified, the new modules are preserved in multiple other brain regions affected in AD. We compare mRNA and protein changes within the same tissues samples, and find that while global mRNA and protein abundance changes in AD are moderately correlated, a number of protein network modules that are highly correlated to AD phenotypes are not observed in RNA networks. We highlight where in the AD protein network recently nominated AD therapeutic targets and fluid biomarkers reside. This deeper protein network can serve as a resource for future AD therapeutic target and biomarker discovery efforts.

527. Life-Threatening Definitive Toxoplasmic Encephalitis as the First Manifestation in HIV Infections — Identification through Clinical and Paraclinical Features

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Objective: Diagnose toxoplasmic encephalitis and review literature for consensus guideline for the diagnosis and treatment.

Background: Toxoplasmic encephalitis (TE) is caused by *Toxoplasma gondii*. TE is the common cause of brain abscess in patients with AIDS. A provisional diagnosis can be made if the patient has a CD4 count<100 cells/microL, has not been receiving effective prophylaxis for toxoplasma, and has a compatible clinical syndrome with positive serology and typical radiographic appearance on brain imaging.

Design/Methods: We report fulminant definitive TE as the first manifestation in a patient with HIV infection who had significant recovery with treatment.

Results: A middle-aged man was hospitalized for cognitive impairment with behavioral disturbances associated with unintentional weight loss that has worsened over three months. History was notable for remote high-risk sexual behaviors and for working as a wildlife conservationist. Neurologic examination revealed aphasia and flat affect. Laboratory data revealed HIV viral load of 27634 copies/mL, CD4 count of 27 cells/microL, and positive anti-toxoplasma IgG antibodies. MRI showed multiple ring-enhancing lesions. CSF exam revealed 3 WBCs and 330 mg/dL protein. He was diagnosed with presumptive TE and treated with antimicrobial therapy directed against toxoplasma, as well as with antiretroviral therapy and with levetiracetam for seizures prophylaxis. Extensive infectious and oncologic laboratory evaluation was unremarkable. Toxoplasma organisms were identified on brain biopsy specimens. Clinical course was complicated by pneumocystis pneumonia and granulicatella bacteremia, and patient required temporary artificial ventilation and tube feeding. Patient had significant neurologic recovery over subsequent months, except for mild dysarthria and subtle signs of pyramidal tract dysfunctions.

Conclusions: In immunosuppressed patients, TE must be differentiated from other causes of focal neurologic disease. Therapy may be initiated after making a presumptive, rather than definitive, diagnosis of TE. A definitive diagnosis of TE requires the detection of the organism in a biopsy specimen.

528. Whole Genome CRISPR-i Screens Reveal How Loss of TDP-43 Function Causes Neuronal Death

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Nuclear depletion of TDP-43 (*TARDBP*) is an early pathological feature of ALS/FTD, and cell-specific reduction of neuronal TDP-43 expression in mice is sufficient to cause neurodegeneration. These findings indicate that loss of TDP-43 function likely contributes to neuronal death, but the underlying mechanisms remain unclear. TDP-43 appears to regulate myriad aspects of DNA and RNA metabolism, including DNA repair and transcription, RNA splicing, transport and stability, and stress granule regulation. To determine which of these TDP-43 functions were necessary for neuronal survival, we performed whole-genome synthetic lethality CRISPRi screens in human iPSC derived neurons. We identified 62 genes whose toxicity was synergistically worsened by concomitant TDP-43 loss, and 100 genes whose toxicity was buffered by concomitant TDP-43 loss. Top KEGG pathway enrichments for our synthetic lethality hits included splicing, ribosome biogenesis, translation initiation, RNA transport, and DNA repair. To explore how these specific hits related to TDP-43 function, we then performed a series of complementary proteomic and transcriptomic experiments in the same neurons used in our primary screen. Together, these studies yielded detailed maps of TDP-43 biology in human neurons, revealing that TDP-43 loss of function leads to neuronal death through parallel dysregulation of several core cellular pathways related to DNA and RNA metabolism. Our data demonstrate feasibility of genome-wide synthetic lethality screens in human iPSC derived neurons, enabling unbiased identification of causal mechanisms of neurodegenerative diseases. Our findings also suggest that effective therapeutic strategies for neurodegenerative disorders associated with TDP-43 loss will require restoration of normal TDP-43 levels and localization, rather than targeting its individual functions.

529. Glycaemic Control, Diabetic Complications, and Risk of Dementia among 0.5 Million Diabetes Patients: A Cohort Study Using the UK Clinical Practice Research Datalink

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Background: Type 2 diabetes (T2D) and elevated insulin resistance are established risk factors for dementia among older adults. However, it remains unclear whether poor glycaemic control in patients with T2D further increases subsequent dementia risk. Previous longitudinal studies on blood glucose level revealed inconsistent results, and few studies have examined the association between diabetic complications and dementia risk.

Methods: In this large-scale cohort study, we evaluated the association of longitudinal HbA1c level with the risk of dementia incidence in diabetes patients, leveraging the UK Clinical Practice Research Datalink (CPRD) from 1987 to 2018. Patients aged over 50 years with valid HbA1c records after T2D diagnosis were included. Mean and coefficient of variation of long-term HbA1c measurements were also assessed in association with dementia risk. HbA1c measurements recorded within two years prior to dementia incidence were excluded to account for reverse causality bias. In addition, associations between major diabetic complications (hypoglycaemia and microvascular complications) and risk of dementia incidence were examined among T2D patients. Time-varying Cox regressions were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for dementia risk after adjusting for potential confounding factors.

Results: During a median of six years follow-up, 23,746 incident dementia cases were observed among 372,287 T2D patients with post-diagnosis HbA1c records. Longitudinal HbA1c level, modelled as a time-varying exposure, was associated with increased dementia risk (adjusted HR=1.06 (95% CI: 1.02-1.09) per 1% HbA1c increment). Compared to patients with HbA1c values of 6-7%, those with HbA1c

values greater than 10% had a 26% (95% CI: 19%-34%) higher dementia risk. Similarly, higher mean and coefficient of variation of HbA1c level during follow-up were associated with higher dementia risk. Among 489,205 diabetes patients with or without post-T2D HbA1c records, those with at least one diabetic complication are at a higher risk of dementia incidence compared to those with no complications (adjusted HR=1.10 (95% CI: 1.07-1.13)).

Conclusions: Higher or unstable HbA1c level and presence of diabetic complications in T2D patients are associated with increased dementia risk. Proper management of glycaemic level and complications are essential for the preservation of cognitive health and prevention of dementia in older adults with diabetes.

530. Mutations in TREM2 Change the Expression Levels of AD-Related Genes

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Variants in TREM2 gene (TVars) is considered to play a vital role in increasing risk of Alzheimer's disease (AD). Further experiments exposed that the complete TREM2 deficiency protected against tau-mediated microglial activation and atrophy, whereas haploinsufficiency elevated expression of proinflammatory markers and exacerbated atrophy. This interesting discovery inspires our speculation, that is, TREM2 changes other genes' expression level and complete loss of TREM2 can repress the changes. Therefore, we integrated multi-omics data using Summary-data-based Mendelian Randomization (SMR) which uses SNPs as instrument variable to infer the causal relationship between AD and SNP-affected gene expression. GWAS and eQTL data were used to identify associations between TVars-influencing genes and AD in transcriptional level, and then GWAS and mQTL data were used to identify associations between methylations at TVars and AD. This process was repeated twice using different GWAS datasets to identify repeating significant loci. Finally, we found 7 genes expression (USP49, RP11-7K24.3, ADCY10P1, TREM2, OARD1, NFYA, and RP11-98J23.8) are related to AD development and this may be caused by 12 SNPs in TREM2. Four of these seven genes are protein coding genes whose relationship with AD is analyzed using single-cell RNA-seq data. This dataset contains 80,660 single-nucleus transcriptomes from the prefrontal cortex of 48 individuals with varying degrees of AD pathology. OARD1, TREM2, USP49's expressions are significant different in neurons and microglia cells between varying degrees of AD pathology (P values range from 1.86e-64 to 0.01). In addition, 10 wild type, 5 $TREM2^{+/-}$ and 5 $TREM2^{-/-}$ mice RNA-seq data were used to do co-expression analysis. We found the expression of OARD1 and USP49 are significant relevant to TREM2's. Further functional analysis of these genes were explored by DAVID and KOBAS which are two authoritative databases. According to the DAVID, the function of ADCY10P1, NFYA and OARD1 are related to late-onset AD. In KOBAS, RP11-7K24.3and RP11-298J23.8 are significant related to nervous system diseases. More than 10 records show that these genes are associated with immune system. The expression levels of these 7 genes affected by TREM2 were significantly related to AD. This could be the key to explain the different effect of complete TREM2 deficiency and haploinsufficiency.

531. A Highly Sensitive Assay Does Not Detect Tau Seeding Activity in the Cerebrospinal Fluid of Alzheimer's Disease Patients

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The templated propagation of alternative, aggregation-prone secondary structures of the tau protein, known as tau seeding, is an important mechanism underlying the progression of Alzheimer's disease (AD) and several other neurodegenerative diseases. Soluble tau seeds represent a promising therapeutic target and direct detection of tau seeds in patient blood or cerebrospinal fluid (CSF) could have powerful diagnostic potential. It is not clear whether seed-competent conformations of tau can be found in the CSF of AD patients. We have produced a new generation of FRET-based biosensor HEK cells for the detection of tau seeding activity that dramatically improves upon the sensitivity of the previous generation. These cells can reliably detect tau seeding activity from extremely small quantities of recombinant tau fibrils or soluble protein from AD frontal cortex or PS19 mouse brain. Tau can be immunopurified from CSF and applied to the biosensor assay without significant signal loss. We used this assay to examine CSF from 11 patients with a clinical diagnosis of AD, most of them confirmed by validated CSF biomarkers. None of the CSF samples produced detectable tau seeding signals despite the assay's high level of sensitivity. This is consistent with reports that CSF contains primarily N-terminal fragments of tau, while the microtubule-binding region near the C-terminus is critical for seeding. Our results indicate that tau seeds may be sequestered from the extracellular space and CSF.

532. History of Seizures in Alzheimer's Disease Patients is Associated with Elevations in mTOR Activity and Neuropathology

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Objective: We hypothesized that epileptogenesis and Alzheimer's Disease are part of a positive feedback loop and that the mTOR pathway is a treatable modifier of AD progression.

Background: Patients with AD have an elevated risk of developing seizures, particularly in patients with familial Alzheimer's Disease (FAD) and severe AD (Samson WN, Eur Neurol 1996). Seizures may worsen AD pathology and hasten the progression of the disease, making their investigation in this population a worthwhile target for intervention (Volicer L, Dementia, 1995).

Design/Methods: Post-mortem temporal cortex samples from 13 control subjects and 34 AD patients (14 with seizure history, 20 without known seizures) were obtained from the Center for Neurodegenerative Disease and Research. Pathological autopsy reports were used to extract disease duration, ventricular enlargement severity, and brain weight at death. Human temporal cortex samples were homogenized and whole cell fractions were obtained. Western blots were performed with the whole cell fractions to measure tau hyperphosphorylation and phosphorylated S6 (pS6) expression, a measure of mTOR activity. Immunohistochemistry was performed with staining for pTau AT100 and pS6 to observe areas of tau hyperphosphorylation and mTOR activity.

Results: Data from pathological autopsy reports showed exaggerated atrophy in AD patients with a history of seizures: a 12% further decrease in brain weight ($p<0.05$) and more severe ventricular enlargement ($p<0.05$). AD patients with a seizure history exhibited longer duration of cognitive impairment (+4.7 years, $p<0.05$), despite no significant differences in the age at death. Seizures may thus be able to unmask AD symptoms at an earlier time point. Seizures were also associated with a significant increase in tau hyperphosphorylation on [Thr212, Ser214] (AT100) ($p<0.01$). PS6 (a readout of mTOR) was elevated in AD patients vs control patients ($p<0.001$) and further increased in AD patients with seizures ($p<0.05$). IHC revealed pS6 colocalized with pTau AT100 suggesting a mechanistic link between mTOR activity and tau hyperphosphorylation. Additionally, tau hyperphosphorylation on AT100 was found to be positively correlated with cognitive impairment duration in the AD cohort ($r=0.74$, $p<0.0001$).

Conclusions: Our study indicates that seizures may exacerbate neuropathology of AD through tau hyperphosphorylation and suggests that AD patients should be evaluated for seizures and treated accordingly. Additionally, rapamycin may be a potential therapeutic target in patients with AD and seizures as mTOR is involved in both epileptogenesis and AD neuropathology.

533. The Association of Motoric Cognitive Risk with Neuroimaging and Incident Dementia: The ARIC Study

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Background: Gait changes are common in older adults and have been linked to cognitive decline and dementia risk. Motoric cognitive risk (MCR), a syndrome characterized by slow gait speed and subjective cognitive complaints, has been associated with dementia risk; however, the neural correlates of MCR, and whether they differ from that of mild cognitive impairment (MCI), remain poorly understood.

Methods: At visit 5 of the Atherosclerosis Risk in Communities (ARIC) study, nondemented participants were classified as cognitively normal, MCR+, and MCI+ (overlapping) based on information from a cognitive exam, functional questionnaires, and a 4-meter walk; MCR diagnosis was based on published criteria and MCI was an adjudicated diagnosis. A subset of participants (N=1645) received a 3T brain MRI at visit 5 to quantify total and regional brain volume, white matter hyperintensity (WMH) volume, and white matter microstructural integrity (WMI) measured by diffusion tensor imaging (DTI). Cox proportional hazards models were used to evaluate the risk of incident dementia after visit 5 (mean follow-up: 4.7 years) associated with MCR+ and MCI+ status, compared to MCR- and MCI-, respectively. Multivariable linear regression was used to compare groups on global and domain-specific cognitive function and MRI variables, adjusted for demographic variables.

Results: Of 5,099 nondemented participants (mean age=75.2; 59% women, 21% Black) included in analyses, 210 were characterized as MCR+ and 1045 as MCI+. MCR was associated with increased incident dementia risk (HR 3.19, 95% CI: 2.43, 4.19); as expected, MCI status was also associated with greater dementia risk (HR 4.24, [3.58, 5.03]). Compared to MCR- individuals, those with MCR demonstrated lower global cognition (Z score: -0.32; [-0.41, -0.24]) and domain-specific cognitive performance (memory, executive function, and processing speed). These cognitive decrements were approximately half of that observed among participants with MCI (Z score: -0.72; [-0.76, -0.69]). MCR, compared to cognitively normal status, was associated with lower total and regional brain volume, greater WMH volume, and reduced WMI. While MCR-associated decrements in brain volume and WMI were generally similar to that of participants with MCI, the MCR-associated increase in WMH volume (0.28 SD; [0.10, 0.47]) was over double that associated with MCI (0.12 SD; [0.02, 0.21]).

Conclusion: MCR is an inexpensive clinical marker of dementia risk. The structural brain abnormalities in MCR are similar to MCI, but notable differences—including greater WMH volume—suggest a distinct neurodegenerative signature.

534. Modeling Ancestry Specific Differences in *APOE* Functionality Using Induced Pluripotent Stem Cell Models

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Background: The *Apolipoprotein E* (*APOE) ε4* allele is the most significant genetic risk factor for late onset Alzheimer's

Disease (LOAD). However, the risk for LOAD in *APOE ε4* carriers is dependent on local genetic ancestry, the ancestral background of a specific chromosomal region around the *APOE* locus. Individuals with local African ancestry around the *APOE ε4* allele have a significantly lower risk for developing LOAD compared to individuals with local European ancestry harboring the same *APOE ε4* allele. Recent studies have examined the function of the *APOE ε4* allele in AD pathology. However, the role of the *APOE ε4* allele in AD pathogenesis in differing ancestral populations remains widely unknown.

Methods: Using *in vitro* models to the recapitulate functionality and genetic signature of ancestry specific lines, we are assessing the effect of local ancestry on *APOE* as it relates to AD pathology. Individuals homozygous for either the *APOE ε4* risk allele or the *APOE ε3* neutral allele from both European and African ancestries were identified, and induced pluripotent stem (iPS) cells were derived. These stems cells were differentiated into cortical neurons and astrocytes, and characterized using immunocytochemistry. A time course analysis of *APOE* expression using qRT-PCR in differentiated cells was performed. Functional analyses of the different cell types included examining differences in amyloid beta (Aβ) production and processing, cholesterol processing, and transcriptional profiling.

Results: A time course analysis showed that *APOE* expression is upregulated in late stage differentiated astrocytes with African ancestry compared to astrocytes of European ancestry at specific time points. *APOE ε4* astrocytes of African ancestry displayed similar Aβ uptake processing as *APOE ε3* astrocytes of European ancestry. These studies will be replicated to validate findings.

Conclusions: Our results suggest pathologic differences associated with the ancestry of individuals surrounding the *APOE ε4* variant. In differentiated astrocytes with local African ancestry, *APOE* expression is upregulated during late stage differentiation compared to astrocytes with European local ancestry. Astrocytes of European ancestry harboring the *ε3* allele and astrocytes of African ancestry harboring the *ε4* allele show similar amounts of exogenous Aβ uptake. Further studies will examine cell-type specific responses within different ethnic populations. Understanding ancestry specific differences in AD pathology can present new opportunities for targeted therapeutic intervention.

535. Nilotinib Effects on Safety, Tolerability, and Biomarkers in Alzheimer's Disease: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial

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This is a single-center, phase 2, randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of nilotinib, and measure biomarkers in participants with mild to moderate dementia due to Alzheimer's disease. Nilotinib 150 mg vs matching placebo was taken orally once daily for 26 weeks followed by nilotinib 300 mg vs placebo for another 26 weeks. Alzheimer's disease diagnosis was supported by cerebrospinal fluid or amyloid positron emission tomography biomarkers. We hypothesized that nilotinib is safe and detectable in cerebrospinal fluid. Nilotinib may alter disease biomarkers and potentially slow clinical decline. Of 117 individuals approached, 13 declined, 51 were excluded, 51 were screened, and 37 were randomized 1:1 to placebo or nilotinib groups. The recruitment period was January 2017 to October 2018 and the trial ended November 2019. Of the 37 individuals enrolled, 27 were women (73%), and the mean (SD) age was 70.7 (6.48) years**.** Nilotinib was safe and well-tolerated, although more adverse events, particularly mood swings, were noted at the 300 mg dose (70.6%) vs placebo (0%) groups (p=.001). In the nilotinib group, amyloid burden was reduced in the temporal (-0.08, 95% CI, -0.21 to 0.01, p=.04) and frontal lobes (-0.19, 95% CI, -2.29 to 0.08, p<0.001) compared to the placebo group. Cerebrospinal fluid Aβ40 was reduced at 6 months (566ng/ml, 90% CI, 135 to 1018, p=.02) and Aβ42 was also reduced at 6 months (52.1ng/ml, 90% CI, -1.0 to 121.8, p=.07) and 12 months (73.9 ng/ml, 90% CI, 14.3 to 137.9, p=.02) in the nilotinib group compared to the placebo. Hippocampal volume loss was attenuated (-27%) at 12 months. Phospho-tau181 was reduced at 6 months (-3.07, CI 90%, -5.92 to 1.18, p=.02) and 12 months (-4.75, CI 90%, -8.03 to 1.76, p=.01) in the nilotinib group. Nilotinib is safe and well-tolerated, and achieves pharmacologically relevant brain concentrations. Biomarkers of Alzheimer's disease were altered in response to nilotinib treatment. These data support a larger, multi-center, phase 3 study to determine the safety and efficacy of nilotinib in Alzheimer's disease.

536. PTPRD Roles Alzheimer's Disease Tau Pathophysiology

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Neurofibrillary tangles (NFTs) are key components of the pathology of Alzheimer's disease (AD). NFT densities correlate well with the extent of AD dementia. NFTs contain hyperphosphorylated tau proteins that misfold and aggregate. Kinases that hyperphosphorylate tau, including the cyclin dependent kinase CDK5 and the glycogen synthase kinases GSK3α and GSK3β, are activated by phosphorylation of their own tyrosines (pY15, pY279 and pY216, respectively). While kinases that phosphorylate these tyrosines are known, the tyrosine phosphatase(s) that dephosphorylate these regulatory phosphotyrosines and thus reduce activities of brain CDK5, GSK3α and GSK3β have not been identified. We now report that the receptor type protein tyrosine phosphatase PTPRD, and other members of its subfamily, can avidly dephosphorylate CDK5, GSK3α and GSK3β phosphopeptides *in vitro* with evidence for specificity. Further, reduced brain PTPRD activity increases levels of phosphorylated GSK3 *in vivo*. These results fit with prior observations that human PTPRD intron 10 SNPs display associations with both a) levels of PTPRD mRNA in postmortem brain samples and b) densities of neurofibrillary pathology in postmortem Alzheimer's disease brains. We also report lead compound positive allosteric modulation of PTPRD's

phosphatase. PTPRD is a novel, druggable contributor to tau pathophysiology in AD

537. Associations between HIV, Antiretroviral Therapy and Risk of Early Onset Alzheimer's Disease

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With robust effects from HIV antiretroviral therapy (ART), the mortality rate in patients with HIV has been drastically reduced and most are able to live normal lives with the HIV viral load controlled by medication. Now nearly half of people with HIV have aged into 50 years or older. As the HIV patient population ages, the prevalence of age-related disorders (including dementia) has increased. While there is solid evidence of HIV-associated neurocognitive disorders (HAND), less is known about HIV and the risk of Alzheimer's disease (AD). In this study, we used the MarketScan® Commercial Claims and Encounters (IBM Watson Health), a national healthcare claims database (2005-2014) of a privately insured population in the United States to assess the risk of early-onset AD among HIV patients ages 64 and younger. We examined medical conditions from the MarketScan inpatient and outpatient databases by the primary or secondary diagnosis code, using International Classification of Diseases, Ninth Revision (ICD-9 code); and procedures/therapies/office visits using Current Procedural Terminology, 4th Edition (CPT-4 code). We examined the prescribed medications from the MarketScan® outpatient pharmacy database using generic drug names and national drug codes. We identified 74,144 patients with HIV, who had enrolled in the database for at least one year during our study period and were at least 50 years older at some point during our study period. Nearly half (44.3%) of them did not receive ART during our study period. There was an elevated prevalence of AD in patients with HIV (0.11%), compared to those without HIV (0.07%). Prevalence of early-onset AD was even higher among those without ART treatment (0.16%). In contrast, the prevalence of AD among those treated with ART was the same as individuals without HIV (0.07%). Multivariable logistic regression analysis confirmed that HIV infection was associated with higher risk of early-onset AD (adjusted Odds Ratio [aOR]: 1.56; 95% Confidence Interval (CI): 1.24-1.97); and ART treatment was associated with lower AD risk (aOR: 0.50; CI: 0.30-0.81), after adjusting for heart disease, hypertension, diabetes, age, gender and other demographic variables. Further studies are warranted for not only delineating the causal link between HIV infection and early-onset AD, but also assessing the potential protective effects of ART treatment on risk for AD.

538. Longitudinal Anatomic, Functional and Molecular Characterization of Pick's Disease Phenotypes

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Pick's disease is a 3R tauopathy in which patients typically present clinically with the behavioral variant of frontotemporal dementia (bvFTD) or agrammatic primary progressive aphasia (agPPA). Pick's disease has been associated with frontotemporal atrophy on MRI, although little is known about how these two clinical variants of Pick's disease differ on neuroimaging and how neurodegeneration spreads through the brain in Pick's disease. The aim of the study was to characterize longitudinal MRI and PET abnormalities in Pick's disease and determine how patterns of neurodegeneration differ with respect to clinical syndrome. Seventeen patients with Pick's disease were identified who had antemortem MRI (eight with bvFTD, six with agPPA, one with semantic primary progressive aphasia, one with unclassified primary progressive aphasia, and one with corticobasal syndrome). Thirteen patients had serial MRI for a total of 56 MRIs, seven had [^{18}F]fluorodeoxyglucose PET, four had Pittsburgh Compound B PET and one patient had undergone [^{18}F]flortaucipir PET. Cross-sectional and longitudinal comparisons of grey matter volume and metabolism were performed between the bvFTD and agPPA cases, and matched healthy controls. Cortical Pittsburgh Compound B summaries were calculated to determine beta-amyloid positivity. The bvFTD cases showed volume loss and hypometabolism bilaterally in prefrontal cortex and anterior temporal lobe, with progressive involvement of posterior temporal lobe over time. The agPPA cases showed volume loss and hypometabolism predominantly in left inferior frontal gyrus, insula, orbitofrontal cortex and supplementary motor area, with progression into prefrontal cortex and anterior temporal lobe observed over time. bvFTD showed greater volume loss and faster rates of atrophy in prefrontal and temporal regions than agPPA. Both groups showed atrophy in bilateral inferior frontal gyrus, left insula, and left inferior temporal gyrus, and spread in individual patients into inferior parietal and motor cortices. Hypometabolism also showed spread into posterior temporal and parietal regions in individual patients with both syndromes. One patient (20%) showed beta-amyloid deposition on PET, and the flortaucipir PET showed elevated uptake in frontotemporal white matter. Patterns of atrophy and hypometabolism differ in Pick's disease according to presenting syndrome, although a set of regions were involved in both syndromes and patterns of neurodegeneration appear to converge to some degree over time.

539. A Randomized, Placebo-Controlled, Double-Blind Trial of the Plasma Fraction GRF6019 in Severe Alzheimer Disease

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Background: The plasma fraction GRF6019 shows multiple benefits on age-related changes in the mouse brain, including improved memory, increased cortical neuronal activity, enhanced synaptic density and neurogenesis, and reduced neuroinflammation. The ALK6019-202 trial (NCT03765762) evaluated the safety and tolerability of GRF6019 in severe Alzheimer's Disease (AD).

Method: The main inclusion criteria were age 60-95 years; probable AD according to NIA-AA criteria; Mini Mental State Examination (MMSE) score 0-10; and a stable dose of AD medications for > 8 weeks prior to baseline. Each subject received 1 daily infusion of 250 mL GRF6019 or placebo (2:1 randomization) for 5 consecutive days and was followed for 4 weeks thereafter. Study drug allocation was blinded to subjects, caregivers, raters, and investigators. The primary endpoint was safety and tolerability. This study was not designed or statistically powered to detect an efficacy signal. Secondary endpoints included the MMSE, the Severe Impairment Battery, the ADCS Activities of Daily Living Inventory for Severe AD, the ADCS Clinical Global Impression of Change Caregiver Input, and the Neuropsychiatric Inventory. The study was conducted at 4 U.S. sites in 2019.

Result: 43 subjects were screened, and 26 subjects (16 women, 10 men; mean age 73.5) were randomized. GRF6019 infusions were very well tolerated. There were no serious adverse events or deaths and no dropouts. In the GRF6019 group (n=18) there were 16 treatment-emergent adverse events (TEAE) in 8 subjects (44%), and in the placebo group (n=8) there were 6 TEAEs in 3 subjects (38%). There were no statistically significant differences at the end of the study in any secondary efficacy endpoints.

Conclusion: This trial demonstrated that daily infusions of 250 mL GRF6019 for 5 consecutive days is safe, well-tolerated and feasible in individuals with severe AD. The excellent safety profile supports continued development of plasma fractions for the treatment of AD.

540. Isolation of PU.1 Positive Nuclei from Post-Mortem Human Brain Allows Better Differentiation of Microglia Subtypes in Alzheimer's Disease

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Microglia-mediated neuroinflammation is thought to contribute to disease progression in neurodegenerative diseases such as Alzheimer's Disease (AD). Recent single-cell RNAseq studies on myeloid cells sorted from mouse brain have highlighted the heterogeneity of microglial subtypes including the presence of homeostatic, age related and disease associated microglia. Isolating microglia from frozen archived human autopsy brain tissue to similarly examine microglia subtypes and their transcriptomic profile using single nuclei RNAseq has not been reported. We compared variables including dissociation methods, fixation methods, and immunolabeling procedures to optimize microglia isolation from frozen human brain. Our study utilized post-mortem brain tissue from 5 male and 10 female participants with an average age of 82.53 years. Six individuals were clinically diagnosed controls confirmed by the absence of AD pathology. Six individuals were clinically diagnosed with dementia and confirmed by the presence of AD pathology. Three individuals were clinically diagnosed as controls but had confirmed AD pathology upon post-mortem analysis. For two pathology positive cases and two pathology negative controls, we performed single nuclei RNA-seq (snRNAseq) on the unsorted nuclei within the prefrontal cortex tissue using the 10X Genomics Chromium platform. For those four and all the remaining individuals, nuclei were isolated from prefrontal cortex as before, and then sorted for PU.1 expression using FACS prior to snRNAseq. We analyzed transcriptomic sequence using the Seurat platform to identify microglia clusters. Our FANS sorting approach yielded larger numbers of cells annotated as microglia with high quality sequence compared to unsorted alone. Our results indicate that sorting for PU.1 expression increases the heterogeneity of the microglia detected in transcriptomic data from human brain. We are able to identify additional clusters that have differential gene expression in the PU.1 sorted data than in the microglia population identified when tissue was unsorted. The results of these analyses indicate that isolating a single cell type for transcriptional analysis provides power in identifying cell-type specific subtypes. This is especially crucial as the field looks to identify subtypes of microglia that can be the targets of pharmacological intervention to prevent neurodegeneration and dementia.

541. Optimizing Aging in Flint Michigan Framework: Exploring Opportunities to Facilitate Successful Aging

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Background: Older African Americans/Blacks experience greater disability than their white counterparts. Despite this, limited information is available on successful aging in minority and underserved communities. In this context, we aimed to understand barriers and facilitators to successful aging among older adults in Flint, MI.

Methods: Through a community based participatory research (CBPR) approach, we conducted a qualitative study to explore determinants of successful aging in Flint. Sampling strategy included three cohorts of older adults, including those that: 1) live at a senior living facility (SLF), 2) do not live at an SLF, but regularly attend a senior center, and 3) neither live at an SLF nor regularly attend a senior center. We conducted focus groups that lasted about 1-hour which were recorded and transcribed. Transcripts were analyzed by three independent coders using a grounded theory approach. We then created a conceptual framework to visually represent our findings.

Results: From June to August 2018, 5 focus groups were conducted, during which 49 older adults participated. Participants were predominately African American and women. Six themes representing determinants of quality of life emerged from the data: Environment, Assistive Services, Economics, Information, Social, and Self. The most common barriers to successful aging identified were healthcare-related, followed by finances and resources.

Conclusion: Older adults are impacted by social determinants of health. Bold yet sustainable ideas, such as bringing healthcare to older adults living in senior living facilities are likely needed to address the social determinants of health among older adults in Flint.

542. DIAN-TU Alzheimer's Disease Prevention Trial of Solanezumab and Gantenerumab: Amyloid, Tau and Neurodegeneration Outcomes

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Alzheimer's disease (AD) prevention trials aim to intervene prior to significant neuronal loss, brain damage, and symptom onset to delay or slow cognitive decline. In dominantly inherited AD (DIAD), mutation carriers develop symptomatic AD at predictable ages with near 100% penetrance. In 2012, the Dominantly Inherited Alzheimer Network Trials Unit Adaptive Prevention Trial (DIAN-TU APT) platform launched a double-blind, randomized, placebo-controlled, parallel group trial of two anti-amyloid-beta monoclonal antibodies, gantenerumab and solanezumab to slow the rate of progression of cognitive impairment in dominantly inherited Alzheimer's disease (NCT01760005). The DIAN-TU scientific development, implementation of the first AD prevention trial, trial challenges and opportunities, including dose escalation, and top-line results will be presented. DIAN-TU enrolled 194 participants at-risk for or with mild symptoms of DIAD in a phase 2/3 trial testing effects of the two treatments on cognitive, clinical, and biological measures of AD for a minimum of 4 years. Amendments increased the dose of each drug, and the trial had a common close in November 2019. Clinical and cognitive measures, MRI, CSF, blood and amyloid, tau and FDG PET scans were studied. Study completion rates of nearly 100% demonstrate the feasibility of comprehensive, long-duration prevention studies in this population. Clinical, cognitive, imaging and biomarker results will be presented for each drug comparing active to placebo and control participants from the DIAN Observational study. Important milestones include developing a platform to enable a comprehensive trial to be delivered in this population, adapting with increasing doses of drugs, developing a disease progression model and inclusion of DIAN observational data to increase the power to determine drug effects. The primary and key secondary outcomes of the DIAN-TU trial will be presented in the context of targeting amyloid-beta at preclinical and clinically symptomatic stages of disease. These results inform about AD hypotheses of causation, timing of treatment and the prospect of slowing or preventing AD in DIAD and sporadic AD.

543. Changes in Cognitive Performance in Patients with Decompensated Congestive Heart Failure

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Background: Patients with decompensated congestive heart failure (HF) are at risk for cognitive impairment due to shared risk factors, or directly resulting from cardiac dysfunction and volume overload. Whether volume status fluctuations in HF patients can transiently impact cognition remains unclear, but would have implications for self-care and monitoring. We tested whether shifts in volume status of HF patients were associated with change in cognitive performance.

Methods: At our institution, stable patients with decompensated HF are treated with intravenous diuretics in an outpatient clinic, with serial diuresis over a number of days. Cognitive testing was performed twice: once, prior to the onset of diuresis (when patients are "volume overloaded") and again when diuresis is completed (at their "dry weight"). Change in weight as a percentage of initial weight was calculated; loss of >=5% initial weight was the primary independent variable. Global cognitive Z-score was the average Z-score for the 5-6 most commonly completed tests, with change defined as: (time2 GlobalZ- time1 GlobalZ). Multivariable linear regression models included demographics, days between testing, and major vascular risk factors.

Results: In 106 HF patients, mean age was 66y; 45% were female and 33% were of black race. Global average cognitive performance at baseline was 0.7 points below a population norm, and on average patients lost 2.4% (6.5 lbs, on average) of their body weight over the course of diuresis (averaging 2.3 days). Overall, change in cognition was not different for those with vs without larger amounts of weight change with diuresis. However, in older (>65 yo) patients, losing >=5% of body weight was associated with a nonsignificant worsening in cognitive performance (unadjusted Beta=-0.28, 95% CI -0.59,0.024), while in younger patients (<65), a similar weight loss was associated with a nonsignificant improvement in cognitive testing (unadjusted Beta=0.39, 95% CI -0.07,0.84); p-interaction=0.014, with similar results in more fully adjusted models, including adjustment for change in mean arterial pressure or change in BUN to creatinine ratio.

Discussion: Although loss of weight (a marker of improved volume status in HF patients) was not associated with improvement in cognition overall, in younger adults there was a suggestion that weight loss in volume overloaded HF patients might be associated with cognitive improvement. Further study is needed, particularly in younger HF patients, to evaluate the impact these transient cognitive changes have on self-care and other aspects of HF care.

544. Biomarkers of Neurodegeneration Strongly Predict Neurocognitive Impairment in Virally Suppressed People with HIV

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Background: As people with HIV (PWH) age on virally suppressive antiretroviral, they become susceptible to neurodegenerative disorders, the most common being Alzheimer's Disease. To evaluate the importance of this relationship, we sought to characterize biomarkers of neurodegeneration and their association with neurocognitive impairment in aging PWH.

Methods: Inclusions were PWH with viral suppression. Those with neurocognitive confounds other than HIV sufficient to explain neurocognitive impairment were excluded. Neurocognitive impairment was assessed using a previously validated, comprehensive battery covering seven domains of cognitive functioning. Overall performance was summarized using the global deficit score (GDS), with higher scores indicating worse performance. Biomarkers measured in blood plasma and cerebrospinal fluid (CSF) using the Simoa platform were neurofilament light (NFL), total tau (t-tau) Abeta42, and Abeta40.

Results: Participants were 271 PWH, mean (SD) age 56.7 (6.62) years, 47 (17.2%) women, 168 (62.0%) non-Hispanic white, median (IQR) CD4 nadir 61.5 (12, 202) and current CD4 454 (277, 667) cells/uL, mean (SD) GDS 0.683 (0.828); 45.6% impaired (GDS > 0.50). HIV-associated neurocognitive disorders (HAND) classification: asymptomatic neurocognitive impairment, 34.8%; minor neurocognitive disorder, 14.8%; HIV-associated dementia, 4.29%. Worse GDS was significantly associated with higher CSF t-tau (Pearson r = 0.340; p = 1.63e-6), lower CSF Abeta40 (r = -0.179; p = 0.0309), and higher plasma Abeta40 (r = -0.192; p = 0.0208). GDS was not associated with CSF or plasma NFL. In a multivariable model, CSF t-tau (p = 1.63e-6) and CSF Abeta40 (p = 0.00136) remained significant, with the full model explaining 17.8% of the variance in GDS (p = 1.03e-6). Older age was associated with increased levels of CSF t-tau. No other demographic variables were related to biomarkers. In a multivariable model with CSF t-tau and CSF Abeta40, age was not significant (p = 0.504).

Conclusions: Strong associations between biomarkers of neurodegeneration and neurocognitive impairment in virally suppressed, cognitively unconfounded PWH highlight the emerging role of age-related neurodegeneration in this population.

545. Morphologic Changes in Regional Brain Volumes during Healthy Aging Process through Automated Brain Segmentation

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Objectives: Age-related differences in regional brain volumes provide useful reference for neurological disorders. We tried

to explore morphometric variation in healthy adult brains as a normative dataset.

Methods: T1-weighted MRI covering the entire brain were acquired for 592 healthy adults aged 21-70 years (238 men, 354 women). Recruitment was done between March 2016 and April 2020 from a tertiary hospital in Korea. They were classified into 5 groups, depending on every 10 years, who had no history of hypertension, diabetes, drug/alcohol abuse, and neurological or psychiatric conditions. All subjects were scanned in five 3.0 T scanners (Phillips). Cortical reconstruction and volumetric segmentation from 3D-T1 axial images were estimated using the Freesurfer image analysis suite (v6.0). Exclusion of the outliers from the raw data and the correction of the intracranial volume were done. To investigate whether the each normalized volume was varied by sex and age group, multiple linear regression model was used. The significance of the interaction term between sex and age was assessed to probe that the volume change with age was differed by sex. We performed the trend test whether the volume changed with age. By defining index of laterality, we further explored that the laterality was varied by sex and age.

Results: The volume of thalamus proper, caudate, putamen, pallidum, hippocampus, amygdala, cortex, total gray matter, subcortical gray matter, and right cerebellum cortex is statistically larger in men than those of women in every age group and showed smaller in women compared to men in every 10 years after the age 40, when compared to the volume of age 20. The both side of amygdala, putamen, and cortex showed significant differences of the decrease of volume as aging process. The right side of hippocampus, right thalamus proper also showed the same trends. But the both side of lateral ventricles and inferior lateral ventricle showed significant differences of the increase of the volume as aging process. In terms of laterality, caudate showed statistically consistent decrease as aging process in men and women, and hippocampus did in women only. But cortex of cerebellum showed statistically consistent increase as aging process in men.

Conclusion: Our results showed the regional brain volumes differs as aging process in gender and laterality. These findings could serve an informative reference as a normative dataset for neurologic disorders.

546. Human Gastrointestinal (GI) Tract Microbiome-Derived Neurotoxins - Contribution to Inflammatory Neurodegeneration in Alzheimer's Disease (AD) Brain

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The human gastrointestinal (GI)-tract microbiome is a rich and dynamic source of microorganisms that together possess a staggering complexity, diversity and individual variability. GI-tract microbes possess a significant potential in secreting what are amongst the most neurotoxic and pro-inflammatory biopolymers known. These include lipopolysaccharide (LPS), enterotoxins, microbial-derived amyloids and small non-coding RNA (sncRNA). One of the major microbial species in the human GI-tract microbiome, about ~100-fold more abundant than *Escherichia coli*, in deep GI-tract regions is *Bacteroides fragilis*, an anaerobic, rod-shaped Gram-negative bacterium that secretes: **(i)** a particularly potent, pro-inflammatory LPS glycolipid subtype (BF-LPS); and **(ii)** a hydrolytic, extracellular zinc metalloproteinase known as *B. fragilis* toxin (BFT) or *fragilysin*. Continuing studies support multiple observations that BF-LPS and BFT (*fragilysin)* disrupt both paracellular and transcellular barriers by cleavage of intercellular proteins, such as E-cadherin, between epithelial cells, resulting in '*leaky*' barriers. These barriers: **(i)** become defective and more penetrable with aging and disease; and **(ii)** permit entry of microbiome-derived neurotoxic biopolymers into the systemic circulation from which they can next transit the blood-brain barrier (BBB) and gain access into the brain where they accumulate and alter neuronal gene expression. This presentation will highlight some recent advances in this extraordinary research area that links the pro-inflammatory exudates of the GI-tract microbiome with innate-immune disturbances and inflammatory signaling within the human central nervous system (CNS) with reference to Alzheimer's disease (AD) wherever possible.

547. The Impact of Dual GRN and TMEM106b Knockout on Neuronal Survival and TDP-43 Pathology

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Introduction: Age of onset and disease duration is highly variable in frontotemporal dementia (FTD) due to progranulin (GRN) mutations and predicted by neither specific mutations nor parental age of onset (Ramos Alzheimers Dement 2020). Polymorphisms in TMEM106b significantly modify the age of onset of dementia in GRN-FTD (Cruchaga Arch Neurol 2011). Studies suggest that the risk allele is associated with higher TMEM106b levels. However, TMEM106b partial knockdown fails to prevent pathological changes in GRN haploinsufficient mice (Nicholson J Neurochem 2013; Arrant Molec Neurodegen 2018). The mechanism through which TMEM106b alters GRN pathology in FTD remains a fundamental knowledge gap (Nicholson, Acta Neuropathol., 2016). We hypothesize that the major allele of TMEM106b is disease permissive in the setting of GRN mutations due to a loss of function.

Methods: Using CRISPR inhibition technology, we will selectively knockdown GRN and TMEM106b in human iPSC-derived neurons using highly effective and previously validated sgRNAs. The sgRNAs encode nuclear fluorescence tags to facilitate confocal imaging of successfully transduced neurons. We will compare the effects of GRN knockdown, TMEM106b knockdown, and dual gene knockdown on neuronal survival through longitudinal imaging. Cells will then be fixed and immunostained for TDP-43 to compare pathologic burden across samples.

Discussion: This is the first human cell model of TMEM106b loss of function and will lay the groundwork for future investigations into the role of TMEM106b polymorphisms in GRN-FTD. Clarifying disease mechanism is critical to advance the field and will identify a potential new therapeutic target, with applications in GRN-FTD and across TDPopathies.

548. Association between Serum Bicarbonate Levels and Cognitive Function among Older Community Dwelling Adults

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Background and Objectives: The kidneys play an important role in the regulation of acid-base metabolism. Low serum bicarbonate levels have been associated with cognitive impairment, specifically executive function, in patients with hypertension (HTN) and chronic kidney disease (CKD). We aimed to determine the association between serum bicarbonate levels (as a measure of metabolic acidosis), and cognitive function in an on-going prospective cohort study of community residing older individuals.

Methods: We used data from the Einstein Aging Study (EAS), a longitudinal cohort study of cognitive aging and dementia in community dwelling adults, 70 years of age and older. All participants with serum bicarbonate levels and cognitive function testing were included in our analysis (n=951). We defined metabolic acidosis as serum bicarbonate level ≤24 mEq/L. Baseline characteristics of participants with serum bicarbonate levels ≤ 24mEq/L and >24mEq/L were compared using descriptive statistics. A multivariable linear regression model adjusted for demographics, comorbidities, medications, and eGFR evaluated the cross-sectional association between bicarbonate levels and cognition at baseline.

Results: The mean age of participants was 79 years (SD 5.0), 62% were female, 63% were non-Hispanic white. There were no significant differences between participants within the 2 groups with and without metabolic acidosis except for diabetes, eGFR, and use of diuretics. Mean serum bicarbonate level was 25meq/L (SD 2.6). We found that low serum bicarbonate levels (≤ 24mEq/L) were associated with better performance on Trail Making Test part A (TMT-A) and Block Design. For TMT-A, completion time for those with serum bicarbonate levels ≤24 was 55.2 sec (SD 22.2) vs 59.4 sec (SD 28.2), p= 0.02. For Block Design, the mean score was 24.8 (SD 9.3) vs 23.1 (SD 8.8) for participants with serum bicarbonate levels ≤24 (p=0.005). The association with attention and executive function persisted after multivariable adjustment (p=0.03 and p= 0.008 respectively). There was no association between serum bicarbonate levels and the domains of memory and language.

Conclusion: In a large cohort of older community dwelling adults, low serum bicarbonate levels were associated with better executive function, attention and visuospatial performance even after adjustment for important covariates.

549. Changes of Metabolic Connectivity in Visual Hallucinations Due to Dementia with Lewy Bodies

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Background: Recurrent complex visual hallucinations (VH) are common in dementia with Lewy bodies (DLB). Predisposition to VH may be related to abnormal neural interactions within and between large scale networks involved in visual function and visual attention. However, the evidence to-date comes from indirect measures of neuronal activity, e.g. EEG or fMRI connectivity. Here we test this hypothesis using a more direct measure of neuronal dysfunction, namely variations in regional metabolism and metabolic connectivity, or the covariance of regional metabolism across subjects, measured with 18F-FDG-PET and graph theory.

Methods: Twenty-six patients with a diagnosis of probable DLB (13 with visual hallucinations (VH) and 13 without (NVH); mean age: 72.9±6.87yrs versus 70.2±7.96yrs) were studied with T1-weighted MRI sequences and simultaneously acquired FDG-PET using a hybrid PET/MR scanner. MRI and FDG-PET data were processed using the Freesurfer/PET-surfer standard pipeline and the Shaefer-Yeo cortical parcellation. Regional standardized-uptake-values (SUVr) for each ROI corrected for partial volume effect and normalized to the cerebellum cortex, were extracted. Metabolic connectivity was computed at the regional level across subjects. Graph metrics clustering coefficient, strength degree, characteristic path length, and hubs were also computed with the statistical package R.

Results: The ROIs of the dorsal attention (DAN) and visual networks showed a significantly lower SUVr in the VH than NHV group ($p<0.01$). Metabolic connectivity showed decreased correlation within the DAN, DMN, but increased correlation within the ventral attention network (VAN) in the VH group. Between-network connectivity increased for regions of the VAN but decreased for visual and DMN regions. Graph metrics showed in VH, as compared to NHV ($p<0.05$) a lower degree of connectivity in regions of the DAN, DMN, and visual network. Conversely, regions of the right insula and orbito-frontal cortex part of the VAN and Limbic Network, respectively, were more strongly connected. Clustering was increased in both VAN and DAN ($p<0.05$).

Conclusions: This analysis shows that VH in DLB are associated with a significant decrease of neuronal activity in regions of the DAN and visual network coupled with a decrease of their within-network metabolic connectivity. Loss of connectivity in visual and attention networks was apparently related to a relative increase of connectivity between neighbouring regions of the VAN (insula) and limbic (orbito-frontal) network. This study is the first metabolic network study of DLB with or without visual hallucinations.

550. Tau and Amyloid Relationships to Resting-State Functional Connectivity in Atypical Alzheimer's Disease

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The mechanisms through which tau and amyloid-beta (Aβ) accumulate in Alzheimer's disease may differ but both are likely related to neuronal networks. We investigated such mechanisms in 58 participants with atypical Alzheimer's disease: 31 with posterior cortical atrophy (PCA) and 27 with logopenic progressive aphasia (LPA). Participants underwent Aβ-PET using Pittsburgh Compound B and longitudinal tau-PET using [18F]flortaucipir, structural and resting-state functional MRI. Three non-mutually exclusive hypotheses on protein spreading were tested: functional network failure via molecular spread (i.e. pathologic proteins spread through functional networks); metabolic susceptibility (i.e. functional hubs are more susceptible to pathologic proteins because of high metabolic demand); trophic failure (i.e. deteriorated functional networks weaken inter-regional trophic support, allowing pathologic protein spreading). For each one of the 210 cortical regions of the Brainnetome atlas, we calculated: functional connectivity to the disease epicenters (regions with the highest mean Aβ and tau uptake in each syndrome); the degree, which is the number of functional connections in graph-theory; the clustering coefficient, which quantifies functional connectivity between neighboring regions in graph-theory; the sum of the functional connectivity values, multiplied by the tau level of the connected regions, as proposed in a recent study. Functional connectivity measures were related to tau and Aβ-PET uptake using Pearson's correlations on group-average data and a mixed-effect model on longitudinal tau data. Regions with high levels of Aβ had a high degree in both syndromes, and hence were more likely to be functional 'hubs'. Regions with high levels of tau were more likely to have low clustering coefficients in both syndromes, suggesting lack of trophic support. Regions strongly functionally connected to disease epicenters were more likely to have higher levels of tau and, less strongly, of Aβ in both syndromes, suggesting that tau more than Aβ spreads through functional networks. The rate of tau accumulation related to functional connectivity measures differently than baseline tau. Tau accumulation in a region was associated with the level of tau in the functionally connected regions, in support of tau accumulation in a functional network, more strongly in LPA. In both syndromes, tau accumulation was moderately correlated to the degree. This study elucidates the relations of tau and Aβ to functional connectivity in two atypical variants of Alzheimer's disease, strengthening the hypothesis that the spread of these proteins is driven by different biological mechanisms related to functional networks.

551. The Aphasic Presentation of Diffuse Lewy Body Disease

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Diffuse Lewy body disease (DLBD) clinically manifests as dementia with any combination of parkinsonism, psychosis, rapid eye movement (REM) sleep behavior disorder and autonomic dysfunction. Cognitive deficits are said to disproportionately affect attentional/executive and visuospatial function and relatively spare episodic memory and language. We present clinical, neuroimaging and neuropathological features of six patients who were all evaluated by a behavioral neurologist and speech and language pathologists and had presented with a progressive aphasia syndrome and had DLBD. All patients were male; median age at onset and death [range] (63[54-84] and 69 [6-90]); 4(67%) had a family history of a neurodegenerative disorder although *SNCA* gene testing was negative. Clinical presenting features included impaired single-word retrieval in spontaneous speech and naming (Western Aphasia Battery [WAB]-Aphasia Quotient - 85.1[69.5-89.8]), impaired repetition of phrases and sentences (WAB-Repetition - 8.4[7.6- 9.2]) accompanied by phonologic errors with spared motor speech, word/object knowledge and agrammatism. At initial evaluations, median Mini-Mental Status Examination score was 24 [11-26]; Montreal Cognitive Assessment - 18[7-18], Frontal Behavioral Inventory - 32 [23-35], Movement Disorder Sponsored -Unified Parkinson's Disease Rating Scale-III - 5[0 - 13] and none met diagnostic criteria for probable dementia with Lewy bodies (pDLB). Overtime, some clinical core features of DLB developed with one patient (17%) meeting probable DLB criteria prior to death and two (33%) meeting criteria for possible DLB. One patient had a history suggestive of possible REM sleep disorder and later developed parkinsonism and fluctuations with a positive dopamine transporter (DAT) scan; another with illusions and possibly visual hallucinations developed Capgras and Othello delusional syndromes, and the third developed parkinsonism but no other symptoms 5 years after onset. Most patients performed poorly on executive function, visual perception and constructional praxis tests. On MRI, diffuse cortical atrophy was observed, with a focus of involvement in the left lateral temporal lobe in two. Mixed pathologies were commonly observed with two patients (33%) having low likelihood, three (50%) intermediate likelihood, and one (17%) high likelihood Alzheimer's disease neuropathologic changes. Additional pathologies included TDP-43 proteinopathy (67%); cerebral amyloid angiopathy (83%) and arteriolosclerosis (50%). Diffuse Lewy body disease can present as a progressive aphasia in the absence of distinct focal areas of atrophy on MRI. Presence of aphasia, therefore, should not exclude underlying Lewy body disease.

552. Accelerated Rate of Hippocampal Atrophy 17-Years Prior to Death in Alzheimer's Disease is Linked to TAR DNA Binding Protein 43

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Alzheimer's disease is characterized by the presence of beta-amyloid in senile plaques and tau in neurofibrillary tangles;

hippocampal atrophy is a well-known feature of the disease. Over the past decade, TAR DNA binding protein 43 (TDP-43) has become recognized as an integral part of the Alzheimer's neurodegenerative process being linked to episodic memory loss, hippocampal atrophy and the presence of the apolipoprotein epsilon 4 allele. It is unknown at present whether TDP-43 is linked to acceleration of hippocampal atrophy rate in Alzheimer's disease, and if so whether such acceleration of rate occurs far from death or close to death. We determine the non-linear trajectory of hippocampal atrophy over time and assessed whether TDP-43 stage is associated with acceleration or deceleration of atrophy rate. One thousand six hundred thirty-eight antemortem volumetric head MRI scans from 557 autopsy confirmed cases with Alzheimer's disease neuropathologic changes, spanning 1-17 years of disease duration prior to death, were analysed. We performed TDP-43, tau and beta-amyloid immunohistochemistry and constructed protein stages. Hippocampal brain volumes were determined using longitudinal FreeSurfer. Bayesian bivariate-outcome hierarchical models were utilized to estimate associations between TDP-43 and hippocampal atrophy over time accounting for Braak neurofibrillary tangle stage (NFT) and CERAD senile plaque score. Of the 557 cases, 284 (51%) were female and 248 cases (45%) were TDP-43(+).We found higher TDP-43 stage to be associated with acceleration of hippocampal atrophy more than a decade prior to death, with deceleration occurring closer to death. Conversely, we found lower TDP-43 stage to be associated with slower early rates of atrophy but later acceleration closer to death. This later acceleration was tightly linked to Braak neurofibrillary tangle stage. The associations with TDP-43 and Braak NFT stage were independent of whether the Alzheimer' disease neuropathologic changes were mild or moderate-severe. The findings suggest that TDP-43 is strongly associated with changes early in the atrophic process with strong relationships throughout the last 17 years of life. It also appears that the proteins, TDP-43 and tau, have different contributions to acceleration and deceleration of the rate of hippocampal atrophy over time in Alzheimer's disease. These findings have important implications for therapeutic approaches that are targeting these proteins.

553. Tauopathy-Induced Gliovascular Dysfunction Identified by Cell-Specific Viral TRAP-seq

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Increasing evidence suggests that the inciting pathogenic events in Alzheimer's disease may involve disruption of the multicellular interactions within the neurovascular unit. The interruption of specific molecular pathways within the neurovascular unit occurs antecedent to classic pathology and therefore is an attractive target to modulate neurodegeneration. However, the majority of molecular pathways regulating neural and gliovascular signaling remain unknown. Single-cell and whole tissue gene expression approaches have been used in various animal models of dementia to discern new pathways but are limited by sequencing depth and spatiotemporal accuracy of transcriptional profiling. We developed an approach for identifying relevant and novel pathways within the multicellular environment of the neurovascular unit interactions in Alzheimer's disease. Cell-specific viral constructs coding for antigen-tagged ribosomes (TRAP) were used to study variance in spatial and temporal gene expression patterns within and between cell types in the PS19 (P301S) transgenic model of tauopathy. The engineered lentiviruses and adeno-associated viruses express an HA-tagged ribosomal protein (Rpl10a-HA) driven by a cell-type specific promoter (Synapsin, GFAP, or PDGFRa) for the major cell types of the neurovascular unit. We demonstrated the ability of the viruses to target specific cell types under particular spatiotemporal conditions and confirmed cell-specificity *in vivo* using both known cell-specific markers and novel markers identified by sequencing. We then combined this cell-specific vTRAP system with the PS19 mouse model of tauopathy to generate multiple cell-type specific transcriptomic databases of the neurovascular unit across several pathologically-relevant time points. Gene ontology analysis indicates a prodromal drive by gliovascular cells including pericytes and astrocytes to support injured neurons. This occurs through specific and temporally regulated coordination of multiple molecular programs driving neuronal differentiation, neurite outgrowth, and synaptogenesis. This suggests a paradigm for gliovascular rescue of neurodegeneration phenomena and implicates numerous novel perivascular molecular pathways in the pathogenesis of tauopathy and Alzheimer's disease.

554. Varied Clinical Presentations of a Rapidly Progressive Disease, Creutzfeldt Jakob - A Diagnostic Challenge

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Creutzfeldt-Jakob disease (CJD) is a rare and fatal disorder with rapid neurodegeneration that has an estimated yearly incidence of 1/1 million cases worldwide, and 350 cases in US. CJD is suspected in cases with rapidly progressive dementia, especially if accompanied by myoclonus, ataxia and/or visual disturbance. Diagnosis is supported by periodic sharp waves on EEG, positive 14-3-3 CSF assay, hyperintensity in the caudate nucleus/putamen and/or in at least two cortical regions (on DWI or FLAIR MRI) and RT-QuIC. Here, we present two cases of CJD to exemplify varied presentation and the challenges workup presents. First case involves a 62-year-old male who presented initially with 3 months of fatigue, sleep difficulties, progressive dysarthria, diplopia and balance disturbance. Exam showed mild dysarthria, diplopia with lateral gaze, normal strength with ataxic finger-to-nose and heel-to-shin. Initial workup including MRI, lumbar puncture, EMG with repetitive nerve stimulation, paraneoplastic panel and lumbar puncture were inconclusive. Given his oculobulbar symptoms and negative lab studies, sero-negative myasthenia gravis was considered and he was empirically treated with plasmapheresis and pyridostigmine, which mildly improved vision. Progressive symptoms with hoarseness, visual hallucinations, truncal/limb ataxia led to repeat work up. MRI brain then revealed

abnormal restricted diffusion and T2 prolongation in the right corpus striatum, minimal findings on the left caudate and bilateral thalami with sparing of the internal capsule. EEG showed diffuse generalized slowing. Positive CSF 14-3-3 assay with RT-Quic giving a 98% probability. Second patient is a 66-year-old female who presented to the ED with two weeks of right hand tremors, weakness, slowing of speech and dizziness. Exam revealed high BP (200 systolic), effortful speech with apraxia, tremor of the right upper and lower extremities with varying amplitude/frequency and normal strength/tone. Initial brain MRI was reported normal. EEG revealed bilateral paracentral periodic epileptiform discharges with intermittent bursts of rhythmic activity, as patient became more encephalopathic. She was empirically treated with steroids, plasmapheresis, and antiseizure medications without improvement. Repeat MRI revealed supportive evidence for CJD with bright cortical ribboning on DWI and CSF positive for 14-3-3. Similar workup initially resulted inconclusive for both patients, who passed away within months of symptom onset, as expected from this devastating disease. These cases highlight the varied clinical presentations, demonstrating the importance of considering CJD workup in patients with rapidly progressive cognitive decline in order to maximize quality of life.

555. Early Occult Network Dysfunction in Cognitively-Normal *APOE*ε4 Carriers is Associated with Elevated CSF SNAP-25 Levels

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Background: SNAP-25 is a recently described biomarker for synaptic integrity known to be elevated in the cerebrospinal fluid (CSF) in Alzheimer's disease (AD) (Clarke, *Alzheimers Res Ther*, 2019), and in *APOE* ε4 allele carriers with mild cognitive impairment (Wang, *Neurosci Lett*, 2018). We hypothesized that cognitively normal individuals with biomarker levels below established cutoffs for AD would exhibit polysynaptic desynchronization and increased CSF SNAP-25 levels related to the presence of *APOE* ε4. CSF SNAP-25 levels may further correlate with measures of network reorganization as assayed using resting-state functional connectivity (rs-fc) in key brain networks known to be altered in AD: the default-mode, memory, and salience (DMS) networks.

Methods: Using cross-sectional analyses, we examined rs-fc from 74 cognitively normal (Clinical Dementia Rating [CDR] 0) adults (mean age 77.59 years ±7.6 years, 15% *APOE* ε4 carriers, 59% female) with no biomarker evidence of AD brain pathology (normal CSF Aβ42, ptau, tau, and pTau/Aβ42 per Hansson, *Alzheimers Dement.*, 2018 and positron emission tomography (PET) PiB-SUVR). Rs-fc were aggregated into canonical cortical networks based on defined criteria (Power, *Neuron*, 2011). A 298x298 connectivity matrix was generated and was then masked to examine only intra-hemispheric (i.e. lateralized) and inter-hemispheric (i.e. callosal) connections between *APOE* ε4 carriers/non-carriers. Finally, partial correlations were employed to account for known confounds (Brier, *Neurology*, 2014).

Results: *APOE* ε4 carriers exhibited increased CSF SNAP-25 levels ([4.01 vs 5.42], $p = 0.0018$), but not CSF Aβ42, PET-PiB, CSF p-tau, or CSF total-tau compared to *APOE* ε4 non-carriers in our highly selected cohort. Significance remained even after accounting for confounds of age/sex/education ([3.85 vs 5.97], $p = 0.0011$). A relative strengthening of local at the expense of long range connections within the DMS networks was observed ($p = 0.019$). Partial correlations revealed a significant correlation between this rs-fc dysfunction and SNAP-25 levels after accounting for confounds ($r = 0.34$, $p = 0.045$). However, correlation was lost when additionally accounting for carrier status, suggesting that the association between rs-fc dysfunction and SNAP-25 levels was mediated by *APOE* ε4.

Conclusions: We observed that in individuals lacking evidence of AD brain pathology, CSF SNAP-25 is correlated with increases in local, lateralized connections relative to long-range callosal connections in key brain networks. Our results suggest APOE e4 may modulate early synaptic function even in individuals lacking significant amyloid or tau burden.

556. Kv1.3 Channel Expressing Brain Myeloid Cells are a Unique Pro-Inflammatory Subset of Microglia Which Can Be Modulated by Kv1.3 Blockers in Alzheimer's Pathology

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Background: Kv1.3 potassium channels expressed by CNS mononuclear phagocytes(CNS-MPs) are promising therapeutic targets for modulating immune responses in neurological diseases including Alzheimer's disease(AD).

Objective: Our objectives were to define the molecular characteristics of Kv1.3-expressing CNS-MPs, determine whether they originated from resident microglia($CD11b^{+}CD45^{int}$) or CNS-infiltrating monocytes($CD11b^{+}CD45^{high}$), and determine whether treatment with Kv1.3 blockers can modulate microglial neuroinflammatory profiles in mouse AD models.

Methods: CNS-MPs were acutely isolated by mechanical dissociation from amyloid(5xFAD) and tau(P301S) mouse models and two post-mortem AD human brains. Kv1.3 surface expression and phenotypic markers were assessed by flow cytometry in isolated CNS-MPs. Transcriptomic profiles of Kv1.3-high CNS-MPs, resident microglia, and peripheral monocyte subsets were compared using Nanostring profiling of neuroinflammatory pathways. Three-month-old wild-type and age-matched 5xFAD mice underwent whole-body radiation and bone marrow transplantation to create CD45.1/CD45.2 radiation chimeras, and Kv1.3 expression in CD45.1 and CD45.2-positive CNS-MPs was assessed at age 9 months. Three-month-old 5xFAD mice also received sham

or Shk223(Kv1.3 channel blocker) for 3 months. Subsequently, $CD11b^{+}CD45^{int}$ microglia were sorted from both groups and contrasted by transcriptomics.

Results: Kv1.3 channels are selectively expressed by 4-5% of $CD11b^{+}CD45^{+}$ CNS-MPs acutely-isolated from 5xFAD mice and post-mortem human AD brains, but not from P301S mice. Transcriptomic profiling of purified $CD11b^{+}Kv1.3^{+}$CNS-MPs, $Kv1.3^{neg}$ microglia, and peripheral monocyte subsets from 5xFAD mice revealed that $Kv1.3^{positive}$ CNS-MPs express high levels of several canonical microglial markers(Tmem119, Cx3cr1, P2ry12) and are transcriptionally distinct from peripheral $Ly6c^{high}$ or $Ly6c^{low}$ monocytes. However, unlike homeostatic microglia, $Kv1.3^{positive}$ CNS-MPs have relatively lower expression of homeostatic genes and increased levels of glutamatergic and synaptic transcripts and proteins, potentially secondary to phagocytic uptake of neuronal elements. Using CD45.1/CD45.2 radiation chimeras in 5xFAD mice in which bone marrow-derived cells carry the CD45.1 congenic marker, we found that $Kv1.3^{positive}$ CNS-MPs originate from resident microglia($CD11b^{+}CD45.2^{intermediate}$) and not marrow-derived CNS-infiltrating monocytes($CD11b^{+}CD45.1^{high}$). Blockade of Kv1.3 channels for 3 months in 5xFAD mice increased the proportion of CD11c+ myeloid cells in the brain and influenced the RNA transcripts in microglia with increased expression of phagocytic genes and suppression of pro-inflammatory genes.

Conclusion: Our results confirm the microglial-origin and identify unique molecular features of Kv1.3-expressing CNS-MPs. We also provide evidence that immunomodulation by Kv1.3 channel-blockade in AD mouse models results in a protective and the pro-phagocytic phenotype of microglia.

557. Resolving the Aggregate Trends of APOE on Transgenic Alzheimers Mouse Cognition

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Apolipoprotein E (APOE), a widely regarded predictor of Alzheimer Dementia (AD) genetic risk, is a major focus of AD research and therapeutic development. Inconsistent results among studies have made it difficult to define whether APOE,and namely APOE3 and APOE4,represent a gain of toxic function, a loss of neuroprotective function, or both. Risk has been attributed with the inhibition of amyloid beta clearance or promotion of amyloid beta aggregation; increase in tauopathy; impairing microglial responsiveness, lipid transport, synaptic integrity and plasticity, glucose metabolism and cerebrovascular function.A better understanding of the correlation of APOE and cognitive function is important. The objective of the present study was to perform a meta-analysis to assess the aggregate trends of APOE on cognitive function in three populations of transgenic AD APOE mice: APOE knockout (KO), APOE (KI), and wild type (WT) mice. Cognition is defined by mouse escape latency using the standard Morris water maze (MWM) protocol. Using the PubMed search criteria of "Alzheimers Mouse", "Morris Water Maze", and "Latency", 32 peer-reviewed studies met inclusion criteria. A relational database was constructed to curate quantitative data from tables and figures published journal articles using a published biocuration protocol with >99.8% transcription accuracy and strict quality control procedures. The resultant data set contained 1,506 data points from 2,144 mice. To insure over-training in the MWM did not skew results, only the first 5 days of training trials were included for analysis. Standard statistical analysis using two-tailed t-test at an alpha of 0.05 was used for initial assessment to compare the aggregate effect on APOE on the populations of interest. Analysis showed a significant difference in MWM escape latency between APOE KO and WT ($p<0.05$) and between WT and APOE KI ($p<0.05$). However, there was no statistically significant difference between escape latencies of APOE KO and APOE KI mice. These results support the hypothesis that APOE possesses both destructive and protective properties in the etiology of AD. Thus, therapies must focus on finding a homeostatic balance that enhances protective mechanisms and minimizes potentially destructive mechanisms. A more complete assessment of the temporal and multi-factorial system stability is needed to identify therapeutic strategies that optimize APOE-related regulatory homeostasis. Future work will focus on an expanded aggregate analysis of additional temporal and population attributes to identify the most promising strategies.

558. Early-Onset Frontotemporal Dementia in Patient with Retrotransposed Transcript of *Matrin-3* Variant 5: A Case Report

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Frontotemporal dementia (FTD) rarely occurs in individuals under the age of 30 and genetic causes of early-onset FTD are largely unknown. The current study follows a 27 year-old patient with no significant past medical history presenting with two years of progressive changes in behavior, rushed speech, verbal aggression, and social withdrawal. MRI and FTG-PET imaging of the brain revealed changes in the frontal and temporal lobes consistent with FTD. Next generation sequencing of a panel of 28 genes related to dementia and ALS initially revealed a duplication of exon 15 in *Matrin-3* (*MATR3*). Whole genome sequencing determined that this genetic anomaly was, in fact, a sequence corresponding with full-length *MATR3* mRNA variant 5 inserted into chromosome 12 (CH12), flanked by 15 base-pair repeats, indicating retrotransposition of a messenger RNA intermediate. This is a novel mutation of *MATR3,* as the majority of mutations in *MATR3* linked to FTD-ALS are point mutations. Genomic DNA analysis revealed that this mutation is also present in one unaffected first-degree relative and one unaffected second-degree relative. This suggests that the mutation is

either a benign variant or disease-causing mutation with incomplete penetrance, which has been observed in heritable FTD. Epigenetic differences could also be responsible for the pathological differences seen between the patient and asymptomatic relatives who carry the mutation. Retrotransposons are not often implicated in neurodegenerative diseases; thus, it is crucial to clarify the potential role of this *MATR3* variant 5 retrotransposition in early onset FTD.

559. Association Rule Mining to Determine Pharmaceutical and Supplement Usage Associated with Alzheimers Disease

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Prescription drugs and vitamin supplements are hypothesized to play a role in the etiology of Alzheimers Disease (AD). Traditional statistics may overlook potentially relevant prognostic combinations, particularly in sparse data sets. Here we perform association rule mining (ARM), an apriori machine learning algorithm, on a public dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The study objective was to assess the ability of ARM to identify meaningful patterns of pharmaceutical item sets associated with a diagnosis of AD. ARM is commonly used in business to identify associations between items within a transaction (e.g. "customers like you also purchased···"), but has applications in predictive medicine. Here association rules were generated for 48,122 pharmaceutical substances, including commonly prescribed AD drugs (e.g. Aricept and Namenda) and non-AD drugs (e.g. vitamin C, vitamin E, Lipitor, simvastatin, and Zoloft). Mathematical support and lift was used to identify rules for individual or combinations of drugs with unusually high or low usage among AD patients. Though vitamins were prescribed to both cognitively normal and AD patients, vitamin D usage was not found by ARM to be associated with AD. Prior studies have found that persons with low blood levels of vitamin D are twice as likely to develop AD. ARM findings suggest not enough AD patients are being prescribed vitamin D and/or that vitamin D is effective for slowing initial onset of AD. The ADNI study cohort had approximately equal number of men and women in AD groups, but the rules {simvastatin:AD} and {Lipitor:AD} were more strongly supported for the male demographic, which supports prior work illustrating cardiovascular risks are more prevalent among men with AD. Interestingly, while there was high support for the antioxidant vitamin rules {vitamin C:AD} and {vitamin E:AD}. These results indicate, while a high proportion of AD patients are taking vitamin C and E, there is either less than expected benefit on AD onset or C and E treatment was not taken early enough to impact AD onset in this cohort. In summary, ARM is a feasible technique for identifying relationships between prescribed drugs, AD diagnosis, and progression. Future work will expand ARM to look at a greater number of AD epidemiological factors in a larger cohort, and compare these associations to machine learning text mining algorithms to identify causal or associative hypotheses from literature.

K-576. Activity Dependent Regulation Of CaMKII And Local RNA Translation Machinery In The Postsynaptic Density

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The ser/thr kinase ca^{2+}/calmodulin-stimulated protein kinase II (CaMKII) is essential in signaling pathways important for synaptic plasticity that underlie learning and memory. RNA transport and local translation are crucial for neuronal signal transmission and synaptic plasticity. Dysfunction of CaMKII and RNA metabolism have been implicated in numerous neuronal disorders. Synaptic accumulation of CaMKII is triggered by neuronal activity, and local Ca^{2+} signaling induces translation of CaMKII. However, the timecourse for activity-induced regulation of CaMKII in the postsynaptic density (PSD) remains to be fully elucidated. We used dissociated rat primary neuron culture, proteomics, pharmacology, and immunoblotting to investigate the translational mechanisms of CaMKII regulation in the PSD. We discovered changes in total protein and phosphorylation states in the PSD following brief NMDA or KCl treatment. These data suggest that activity-dependent regulation of local RNA translation is induced in the PSD. This study may contribute to understanding of the underlying pathophysiology of neurological disorders and pathways for novel therapeutics.

K-596. Synergistic Behavioral And Neuroinflammatory Effects Of Amyloid Neuropathology And Sepsis Survival In A Murine Model Of Alzheimer'S Disease

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Rationale: Survivors of sepsis frequently experience long-term brain dysfunction. In particular, hospitalization for acute illness is a risk factor for incident dementia. The interaction of neuroinflammation due to sepsis and underlying amyloidosis, therefore, may represent a modifiable risk factor for loss of cognitive resilience and progression of dementia in vulnerable patients. We therefore hypothesized that sepsis survival would result in synergistic worsening of behavioral deficits and neuroinflammation in a mouse model of early, presymptomatic amyloid beta accumulation.

Methods: Alzheimer's disease neuropathology was modeled using male and female 5xFAD mice on a C57BL/6 background. 5xFAD mice were compared to wild-type controls of the same background. Mice underwent CLP at 4-5 months of age, at which time they exhibit amyloid-β deposition but no significant behavioral deficits. Cognitive and affective impairment were studied starting 14 days after CLP using the puzzle box task and contextual fear conditioning. Neuroinflammation was studied by RT-PCR of RNA isolated from whole brain lysates.

Results: Mortality, weight loss, and weight recovery were not different among 5xFAD and wild-type control mice after CLP. In the puzzle box task, which measures latency to escape from a brightly lit open field through successively

more difficult obstacles, performance was similar among wild-type and 5xFAD naïve control mice and wild-type CLP survivors. 5xFAD CLP survivors, however, had worse performance than wild-type CLP survivors ($p = 0.056$). 5xFAD CLP survivors had markedly increased generalization of conditioned fear in a novel context compared to wild-type sepsis survivors ($p < 0.01$). Sepsis survival increased phosphorylated tau, with a specific increase in in 5xFAD sepsis survivors ($p<0.05$), but did not change amyloid beta levels. Constitutive brain expression of multiple proinflammatory genes, including *Tnf, Hif1a, Ctsc, Cfh, C4b* were enhanced 25 days after CLP in 5xFAD CLP survivors compared wild type sepsis survivors and control mice of both genotypes.

Conclusions: Sepsis survival and early amyloid-β neuropathology lead to synergistic, persistent behavioral deficits and neuroinflammation. Ongoing studies more broadly examine the transcriptomic interaction of sepsis survival and amyloid-β neuropathology, as well as the specific role of damage associated molecular pattern signaling via TLR4 and complement deposition in synergistic brain dysfunction.

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Education

560. Necessity of Systems Medicine, Neuroscience Outreach to Combat Covid-19

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Neurological Impact: The coronaviruses can cause nerve damage through direct infection pathways (blood circulation pathways and neuronal pathways), hypoxia, immune injury, ACE2, and other mechanisms. Meanwhile, the coronaviruses have detrimental effects to attack the lung tissue and causes a series of lung lesions such as hypoxia. Furthermore, the coronaviruses can enter the nervous system directly through the olfactory nerve, and also enter the nervous system through blood circulation and neuronal pathways, resulting in neurological disorders.

Systems Biology: In order to tackle the complexities of this disease, a Systems Biology approach can provide insights into the biology of the virus and mechanisms of disease. This is achieved by integration of genomic, transcriptomic, proteomic, and molecular evolution data layers to understand its impact on host cells. It has provided insights into the body's responses to the virus, including a broader view of the role of the Renin- Angiotensin-System, and the likely targeted tissues and cell types that are responsible for COVID-19 symptoms. Integrated models of disease can be generated using data from the literature as well as protein expression and interaction data sets.

Predictive Medicine: The mechanistic and molecular underpinnings of COVID-19 contributes to understanding of evolution of novel coronavirus and its varying effects on human hosts and development of drugs targeting viral and human proteins. Networks at both the cellular/tissue level and organ level are needed to understand the mechanism of drug action and to predict therapeutic efficacy and adverse event probability. Machine learning is used for automated drug discovery including target identification and validation based on gene-disease associations, compound screening and lead discovery, biomarker identification and prediction. Computational approaches such as pathway mapping, genetic association, molecular docking and signature matching can be used for drug repurposing. Drug combinations can be optimized using feedback system control. The best justified drugs for repurposing to treat COVID-19 patients are the host-factor-targeted drugs HCQ, AZ and camostat and nafamostat and the viral RdRp-targeted drugs remdesivir and favipiravir.

Outreach: To this end, I have created a portal https://sars2cov.wordpress.com/ that gives actionable scientific guidance on COVID-19 by SARS-CoV-2. It may be the only such portal that deals extensively with each dimension of the disease succinctly and graphically and caters to everybody from novice to healthcare professionals alike. [1] Prates, ET et al. *Confronting the COVID-19 Pandemic with Systems Biology*. bioRxiv, 2020.

561. Simulation for Neurologic Emergencies and Acute Scenarios (SNES) Course: A 4-Year Evolutionary Experience of Utilizing Simulation for Incoming PGY-2 Neurology Residents to Prepare Them for Independent Calls

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Background: Emergent and acute neurological disorders have a high burden of morbidity and mortality if not recognized and managed early. PGY-2 Neurology residents (PGY2NR) are usually the front-line staff for these neurologic emergencies. They undergo a steep learning curve as they transition from PGY-1(Internship year) into PGY-2. There have been no standardized method to prepare PGY2NR in our institution for independent call. We aim to determine the feasibility of a Simulation for Neurologic Emergencies and acute Scenarios (SNES) course and to demonstrate its utility to improve perceived preparedness of PGY2NR for independent call. We also described the logistics and the evolution of SNES over a 4-year period.

Methodology: As an educational improvement initiative, SNES course was created in collaboration with the University of Mississippi Medical Center Interprofessional Simulation Training Assessement Research and Safety center (ISTARS). SNES course was conducted annually since August of 2016. Scenarios tested included status epilepticus (SE), intracranial hypertension (IH), neuromuscular emergency (NME), acute ischemic stroke (AIS), thrombolytic reversal (TR) and spinal cord pathology (SC) each with components of 1)assessment and plan (AP), 2)management (Mx), 3)presentation to the

attending (PA) and 4)hand-off (HO). The primary outcome measure was mean(±SD) level of perceived preparedness (LPP) for independent call as measured by a 5-point Likert-like scale. Long-term feedback from former PGY-2 Neurology residents (2016-2018) regarding the SNES course were collected. Student t-test was utilized to compare the pre-SNES and post-SNES preparedness scores.

Results: There were a total of 18 PGY2NR in 4 years who participated in the SNES course. The mean LPP was significantly higher in post-SNES for all components of each case scenario except for AIS (AP, Mx, PA and HO) and SC Mx. 100% of former PGY2NR respondents stated that the course helped prepare them for PGY-2 independent call and helped them manage emergent and acute neurologic conditions beyond PGY-2 Neurology year. Annual SNES was found to be feasible and sustainable.

Conclusion: Our institutional SNES course was found to significantly increase the perceived level of preparedness of PGY2NR for independent call for most of the components. Furthermore, it is feasible and sustainable through the course of 4 years. All former SNES course takers had a positive experience. This course is now part of the annual PGY2NR curriculum.

562. Neurological Aspects of Corona Virus Infectious Disease 2019 [COVID-19]

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Purpose of the Review: COVID-19 has spread rapidly around the world and now declared a pandemic by World Health Organization (WHO). Neurological manifestations are being reported in COVID-19 patients but clinical guidelines and effective treatments remain unclear.

Recent findings: There is evidence for neurotropism in previous coronaviruses (CoVs). Current retrospective case series and cohort studies from Wuhan, China have indicated that almost 1/3 rd patients with COVID-19 showed neurological manifestations; older age and comorbid conditions are associated with poor outcome in these patients. Covid-19 patients admitted in the Intensive Care Unit (ICU) revealed a number of laboratory abnormalities.

Summary: Understanding the spectrum of neurological manifestations of COVID-19 and the impact of Covid-19 on patients with underlying neurological conditions may help to improve outcomes.

563. Gender's Influence on Career Success of Physician-Scientists in Neurology

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The objective of this study was to determine the influence of gender on research career success amongst Medical Scientist Training Program (MSTP) graduates in neurology. Ongoing concern over the physician-scientist attrition has attracted significant attention. Research has documented an influx of women training to become physician-scientists over the past decade, but little is known about their research contributions and professional success as physician-scientists. Although many studies have investigated gender disparities in research success in other medical specialties, gender disparity in scientific achievement and professional advancement in neurology and neuroscience has received less attention. Gender differences in research outcomes were measured in a cohort of 108 graduates of the top NINDS and NIH-funded MSTPs from 2000 and 2010. Three research success outcomes were collected from SCOPUS and NIH RePORT for each participant, including 1) h indices, 2) federal grant award rates, and 3) research independence attainment (R01/R21). For each outcome, a comparison of the performance of females versus males was made. MSTP students were predominantly male, with less than 1/3rd being female. The percentage of males and females in the MSTP cohort with grant awards and research independence were similar. A relationship between gender and h index factor was observed, in which males had higher *h* indices. The findings in this study help highlight that in neurology, fewer women than men enter the physician-scientist pipeline through the MSTP training pathway. Because the chance of research success is the same for both men and women with MSTP training, increasing the number of female MSTP graduates seems to be a logical strategy to develop more female physician-scientists and reduce gender disparity in academic neurology.

564. CSF Cryptococcus Antigen Test, Trends and Epidemiology

Sushma Edara, M.B.B.S*, Pradeep Bathina, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

Cryptococcal meningitis is an opportunistic invasive fungal infection caused by Cryptococcus Neoformans or C. Gatti and by far is a major cause of mortality and morbidity in HIV patients. Traditional methods like India ink stain and culture have limited sensitivity when compared to antigen detection. CSF Cryptococcal Antigen test (CCAg) is commonly used for screening, diagnosis and treatment monitoring of meningitis from cryptococcosis in HIV-infected patients. CCAg by lateral flow assay (LFA) has replaced other tests and is highly sensitive (99.3%) and specific (99.1%). Screening and early diagnosis can reduce the development of cryptococcal meningitis and improves mortality and morbidity. However, data is limited to the extent of CCAg test ordering and rate of positivity in clinical practice. Here we present extensive data from a large tertiary care medical center on CCAg testing.

Objective: The aim of this study is to determine the frequency of ordering CCAg testing, rate of positive tests, epidemiological characters and outcomes of the patients with a CCAg positive test.

Methods: We performed a retrospective study of all patients who received the CCAg test at the University of Mississippi Medical Center from January 3, 2013 to December 31, 2019. Patient Cohort Explorer was used to obtain de-identified patient data from EPIC. We obtained

the number of encounters and patients on whom the CCAg test was performed. Further analysis was performed on the de-identified data to study the epidemiology of CCAg testing.

Results/Conclusion: CSF CCAg test was ordered 1,823 times on 1522 patients across 7 years with 216 (11.84%) total positives. All 216 CSF CCAg tests were positive in 89 patients. 181 CCAg tests are positive in 54 HIV patients and 35 CCAg tests were positive in non-HIV patients. All 216 positive tests were hospital encounters when the patient is admitted. Minimum, maximum and median age of ordering test was 0, 89 and 48 while for positive patients the minimum, maximum and median age were 22, 75 and 45 respectively. 851 females and 972 males got the test done (ratio 0.87) while 27 females and 62 male patients are positive (ratio 0.43). 1194 African Americans and 547 Caucasians were tested while 70 African-American and 14 Caucasian patients were positive. Number of positive patients from 2013 to 2019 is 21, 17, 12, 5, 15, 7 and 12 respectively. Of the 89 positive patients, 50 are alive while 39 are deceased.

565. Epidemiology and Outcomes for HIV Patients with Cryptococcal Meningitis

***Sushma Edara, M.B.B.S**, Pradeep Bathina, MD. University of Mississippi Medical Center, Jackson, MS, USA.*

Cryptococcal meningitis is an opportunistic invasive fungal infection caused by Cryptococcus neoformans or C. Gatti and by far is a major cause of mortality and morbidity in HIV patients. Traditional methods like India ink stain and culture have limited sensitivity when compared to antigen detection. CSF Cryptococcal Antigen test (CCAg) is commonly used for screening, diagnosis, and treatment monitoring of meningitis from cryptococcosis in HIV-infected patients. CCAg by lateral flow assay (LFA) has replaced other tests and is highly sensitive (99.3%) and specific (99.1%). Screening and early diagnosis can reduce the development of cryptococcal meningitis and improves mortality and morbidity. Here we present data from a tertiary care medical center about HIV positive patients with Cryptococcal meningitis diagnosed from CCAg.

Objective: The aim of this study is to identify epidemiological characteristics and outcomes of HIV positive patients diagnosed with cryptococcal meningitis by CCAg.

Methods: We performed a retrospective study of all HIV positive patients who had a positive CCAg test at the University of Mississippi Medical Center from January 3, 2013, to March 31, 2020. Patient Cohort Explorer was used to obtain de-identified patient data from EPIC. We obtained the number of encounters of HIV patients on whom the CCAg test was positive. Further analysis was performed on the de-identified data to study the epidemiology and outcomes.

Results/Conclusion: 181 CCAg tests are positive in 54 HIV patients during their 86 hospital admissions with the diagnosis of cryptococcal meningitis. The minimum, maximum, and median age for positive patients were 24, 66, and 45 years respectively. Of the 54 patients, 17 patients are females and 37 patients are males (ratio 0.45), 46 patients were African Americans and 4 patients were Caucasians while 4 patients identified as others. The number of CCAg and HIV positive patients from 2013 to 2020 are 10, 9, 9, 4, 10, 7, 4, and 1 respectively. Of the 54 positive patients, 33 are alive while 21 are deceased. For the 86 hospital admissions, the median length of stay was 15 days with a maximum of 154 days. 51 patients were discharged home while 10 patients expired during their hospitalization. 8 patients were discharged either to SNF/LTAC, 8 patients left against medical advice while 5 patients were discharged on hospice. Of the 54 patients, 25 patients had Medicaid, 13 had Medicare and 11 were Self-pay.

566. Case Report: Rhomboencephalosynapsis - A Unique Congenital Posterior Fossa Malformation

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Background: Rhomboencephalosynapsis is a rare cerebellar anomaly characterized by hypogenesis or agenesis of the cerebellar vermis, fusion of the cerebellar hemispheres, and fusion of the dentate nuclei and cerebellar peduncles. The condition is commonly associated with supratentorial abnormalities as well as aqueductal stenosis and resulting hydrocephalus. Clinical manifestations range from mild truncal ataxia and normal cognitive function to severe deficits in cerebellar function and intellectual disability. This congenital cerebellar malformation may present as an isolated anomaly or in conjunction with more complex syndromes such as Gomez-Lopez-Hernandez syndrome and VACTERL association. We report a case of Rhomboencephalosynapsis in a preterm neonate.

Case Presentation: A preterm male infant was admitted to the neonatal intensive care unit (NNICU) for respiratory distress syndrome and numerous birth defects diagnosed by prenatal ultrasound. On prenatal ultrasound, the infant was found to have lateral ventriculomegaly with an absent septum pellucidum, rhomboencephalosynapsis, incomplete appearance of the corpus callosum, as well as several cardiac defects including a double outlet right ventricle and a subaortic ventricular septal defect. The infant required CPAP in the delivery room, Lasix for diuresis, and naso-gastric tube feeds. He continued to display signs of poor growth in the NNICU, so it was determined that the patient would need to be transferred to a higher level of care facility for placement of a gastrostomy button under cardiac anesthesia.

Conclusion: Rhomboencephalosynapsis is a rare congenital cerebellar malformation that is being diagnosed more frequently using prenatal neuroimaging. Children with rare and chronic medical conditions often experience limitations in self-care functions and have long-term dependence on their caregivers. Juggling the provision of care for a child with chronic health conditions with the challenges of everyday life can be a daunting task for a parent. Hence, the use of prenatal imaging to diagnose conditions such as rhomboencephalosynapsis allows providers to counsel parents on the long-term effects and management of their infant's condition, as well as advocate for the supportive care needs of the parents. Early education and planning regarding the infant's condition will ensure that the child has the best chance for a long, healthy, rewarding life.

567. Utility of Mobile Applications in Clinical Neurology

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Background: Mobile applications (apps) have transformed modern society. With the ever-growing presence of mobile devices there has been a surge in the number of apps that are medically oriented and provide an instant access to the information, calculations, and references.

Objective: To analyze the relevance of currently available mobile apps for clinical neurology and neurological education.

Methods: The apps resulting from search on Apple's App Store and Google's Play Store using keyword "neurology", "stroke," "epilepsy," "movement disorders," "neuromuscular," and "headache" were analyzed for purpose, cost, rating, and most recent update. Data was obtained from March thru April 2020.

Results: A total of 222 unique apps were included in this study. These apps were classified into 4 categories based on purpose: 30 (13.5%) clinician-centered, 46 (20.7%) patient-centered, 84 (37.8%) education, and 62 (27.9%) references. Apps were also classified based on neurologic topic: 138 (62.2%) comprehensive neurology, 7 (3.2%) neuroradiology, 28 (12.6%) Stroke, 6 (2.7%) neuromuscular, 4 (1.8%) neuro-ophthalmology, 4 (1.8%) Multiple Sclerosis, 2 (0.9%) neurodegeneration, 7 (3.2%) movement disorders, 8 (3.6%) Headache, 3 (1.4%) neurocritical care, and 15 (6.8%) Epilepsy. 48 (21.6%) of the apps were found on both stores. Majority of apps were free (86%), but one-third involved in-app purchases. Price of paid apps ranged $0.99-$65.99 (mode $4.99). The mean overall rating was 4.3/5; and 54 (24.3%) apps were lacking any reviews. Of all the apps, there were a total of 26,228 ratings in the App Store, while a total of 740,192 ratings in the Play Store. The mean number of ratings per app was 189 in the App Store, and 5,650 for the Play Store. Within the last year, 97 (43.7%) of the applications had an update released.

Conclusion: There are more than 200 apps relevant to clinical neurology. Most of the apps are targeted to clinicians, and only 20% to the patients. Neurology subspecialty-focused apps were less represented than broad content neurological apps. Majority of the apps were updated within the last year, but some are no longer supported with no obvious usage. Apps on Google's play store have more reviews implying wider use on Android devices versus iOS. As more medical professionals begin using mobile applications for patient-care and as applications increase in purpose and utility, it is pertinent to fully assess the accuracy of the information provided in these applications.

568. Hogwarts House Grouping for a Combined Wellness and Assessment Initiative for Resident Trainees in Neurology (Hogwarts-Neurology)

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Introduction: Physician burnout is prevalent. Up to 61% of Neurologists have been found to have signs of burn out. There is lack of data regarding methods to decrease burnout and improve wellness. In the University of Mississippi Medical Center (UMMC) Department of Neurology, it was noted that the residents had a lack of interest and participation in didactics, likely due to burnout. The Hogwarts School of Witchcraft and Wizardry™ (HSWW) alumni, now faculty in UMMC conducted the *HOgwarts house Grouping for a combined Wellness and Assessment initiative for Resident TraineeS in Neurology (HOGWARTS-Neurology) project*, with the *aim of improving and maintaining resident interest and participation in several Neurology didactics*.

Methods: Utilizing the Plan-Do-Study-Act method, HOGWARTS-Neurology project was initiated on October 1, 2019. The PGY2-4 Neurology residents were instructed to utilize the Pottermore Sorting Hat at https://www.wizardingworld.com/ or be sorted through https://www.proprofs.com/quiz-school/story.php?title=mte2mdawoq2srl. The optimum number of residents in each didactic was calculated at 9 taking into consideration post-call, vacation and/or interview. The 5 Neurology topics selected as the themes for this initiative include critical care of stroke, neuroanatomy, RITE exam review, neurophysiology and movement disorder. The residents were given a minimum of 1 week to prepare for each upcoming activity which may include Jeopardy game, drawing, dancing, acting-out, cooking and baking. Outcome measures included post-session resident survey, participation and attendance during each session.

Results: A total of 12 residents were sorted into the houses with each house having at least 2 residents. The mean number of residents present in each activity was 10 ± 1. The activity with the highest post-session survey response rate (50%) was critical care of stroke (first activity) for which all the residents either agreed or strongly agreed that the activity increased medical knowledge, system based knowledge and facilitated teamwork among housemates. There was attrition noted in the post-session survey response. Resident participation in all activities were high as noted by videos and pictures taken during the sessions. There were also noted additional benefits such as improved house-team-spirit, involvement and interaction among residents and attendings.

Conclusion: The HOGWARTS-Neurology project is a novel method to improve participation, interest and attendance of Neurology residents in Neurology didactics as shown by optimal average attendance and a high-level of participation by the residents. This methodology have now been incorporated into several aspects of our Neurology residency program.

569. Dysphagia from Long-Term Olanzapine Use- A Rare Adverse Effect

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Background: Dysphagia is a rarely reported side effect of second-generation neuroleptic medications.

Objective: The aim of this study is to review the available literature on dysphagia caused by second-generation antipsychotics through an illustrative case report.

Illustrative Case report: A 74-year-old, Caucasian male with a past medical history of mood instability and psychosis, on once-daily clonazepam 0.5 mg, duloxetine 60 mg, and olanzapine 10 mg since 2005; presented to the clinic with complaints of dysphagia for the past 4 years, that has been progressively worsening, and is more pronounced during the end of the day. It started with difficulty swallowing liquids, then progressed to both solids and liquids. He reports frequent drooling, worse with bending forward. He denies pain with swallowing, choking on food, coughing, regurgitation, loss of weight or appetite, and any feeling of food stuck in his throat or chest. On examination, fasciculations were observed on the surface of the tongue. Electromyogram showed no evidence supporting a motor neuron disease. A modified barium swallow study showed moderate oropharyngeal dysphagia characterized by a delayed swallow, impaired laryngeal excursion, impaired pharyngeal clearing, and absent cough reflex with aspiration (thin liquids). Esophageal gastro duodenoscopy and ENT evaluation were reported normal. After discussion, we suggested that his symptoms of dysphagia could possibly be from his long-term use of olanzapine.

Limitation: We suggested a decrease in the dose or switching the drug to another antipsychotic. The patient declined any change to his medication because it controlled his psychotic symptoms well.

Review Method: A literature search was done using the keyword 'second-generation antipsychotics and dysphagia'. All studies in the English language were analyzed for our review.

Review Results: 1. The literature review showed 17 cases of dysphagia with second-generation drugs- clozapine (5); risperidone (5); olanzapine (3- including current case); quetiapine (2); aripiprazole (1); paliperidone (1). 2. Proposed pathophysiology- EPS or an anticholinergic side effect of the drug. 3. Outcomes- weight loss, airway obstruction, and aspiration. 4. Treatment- drug cessation, dosage reduction, or switching to a different medication. **Conclusion:** Dysphagia can occur with any antipsychotic therapy and prompt diagnosis and treatment are essential to avoid fatal complications like aspiration pneumonia and airway obstruction. Unfortunately, our patient denied any change in the medication or it's dose as it helped him with his mood.

570. Research Outcomes in Parkinson Disease Emerging Therapies: Impact of a Medical Education Program on Neurologists' Knowledge

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Introduction: Parkinson disease (PD) is a progressive neurodegenerative disease characterized by both motor and nonmotor symptoms. Although therapies exist to help manage symptoms, none have proven long-term effectiveness in modifying disease progression necessitating continued development of future therapies. It is important that clinicians are made aware of the potential risks and benefits of investigational therapies for PD. A study was undertaken to evaluate the effectiveness of an online educational intervention to improve knowledge and confidence among neurologists for therapies being developed in the PD space.

Methods: The online continuing medical education (CME) activity format consisted of a 30-minute video discussion between three physicians who are movement disorder experts. The educational effect was assessed by comparing a matched sample of neurologists' responses to four identical questions presented before and directly after exposure to the intervention. A chi-square test was used to identify significant differences between pre- and post-assessment responses. Cramer's V was used to calculate the effect size of the online education. Data from the participants were collected between November 26, 2019 and February 4, 2019.

Results: Participation in the CME intervention improved knowledge and there was an adequate effect size among neurologists utilizing the program (n=282; V=.181). The following areas showed significant (P <0.05) pre- vs post-educational improvements: primary outcome for a trial that examined the early vs delayed use of levodopa/carbidopa in patients with early PD (60% relative pre-vs post education improvement), primary outcome for a clinical trial of isradipine in patients with newly diagnosed PD (60% relative pre-vs post education improvement), and identification of primary PD symptoms assessed in a clinical trial of foliglurax (34% relative pre-vs post education improvement). After participating in the activity, 38% of neurologists had a measurable increase in their confidence in differentiating symptoms of wearing-off from symptoms from those of levodopa-induced dyskinesia in patients with PD.

Conclusions: The results suggested that the CME-certified 30-minute video discussion between physician experts was effective at improving knowledge in PD related emerging therapies. Future educational efforts should continue to address findings from clinical and other research in PD.

571. Online Medical Education Improves Knowledge among Neurologists Regarding the Relationship between Age and Immune System Function in Multiple Sclerosis

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Introduction: Multiple sclerosis (MS) is a chronic autoimmune disease defined by demyelination in the central nervous system (CNS) resulting in clinical symptomology including sensory deficits, pain, fatigue, and spasticity. It has been established that the immune system function decreases as people age, an effect referred to as immunosenescence. Less certainty exists regarding how age-related changes in immune function impact MS disease activity and therapeutic selection. A study was undertaken to evaluate the effectiveness of an online educational intervention to improve knowledge and confidence among neurologists regarding our current understand of age related changes in the immune system and how these changes may impact the selection of disease-modifying therapies (DMTs) for the management of MS.

Methods: The online continuing medical education (CME) activity format consisted of a 15-minute video discussion with two physicians who are MS experts. Educational effect was assessed by comparing a matched sample of neurologists' responses to four identical questions presented before and directly after exposure to the intervention. A chi-square test was used to identify significant differences between pre- and post-assessment responses. Cramer's *V* was used to calculate the effect size of the online education. Data from the participants were collected between May 24, 2019 and August 5, 2019.

Results: Participation in the CME intervention improved knowledge as indicated by a considerable educational effect size among neurologists (n=200; *V*=.220). The following areas showed significant (*P* <.05) pre- vs post-educational improvements: the impact of immunosenescence on immune cell populations in a healthy older adult (28% relative pre-vs post education improvement), selection of a DMT in an older adult with MS who has a history of recurring infections (125% relative pre-vs post education improvement), and the consequences of immunosenescence in an older adult with MS which would impact DMT selection (24% relative pre-vs post education improvement). After participating in the activity, 50% of neurologists had a measurable increase in their confidence for understanding how immunosenescence can impact the effectiveness of DMTs for MS.

Conclusions: The results indicated that the CME-certified 15-minute video discussion between physician experts was effective at improving knowledge of the immunosenescence and how this process may impact therapeutic decision-making in MS. Future education efforts should continue to cover advances in our understanding of how immunosenescence impacts MS and related treatment decisions.

572. Brainwave about Brainwaves: A New Educational Initiative for Medical Students

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Introduction: It has been estimated that by 2050, visits by patients with neurological complaints to primary care physicians and neurologists will exceed 73 million. Today's medical students will provide that care. Epilepsy is one of the commonest neurological disorders. The American Academy of Neurology undergraduate subcommittee has recommended that all students gain experience of neuroimaging studies, but there is no recommendation for formal training in EEG or epilepsy for students during their neurology clerkship.

Goals and Objectives: 1. Determine if there is a need for medical students to have an additional curriculum in EEG and epilepsy or if a traditional curriculum is sufficient. 2. Design a structured course to provide this training effectively and in the most efficient and understandable manner.

Methods and Results: We performed a literature search and studied the information regarding medical student clerkship curricula from various universities. The standard curriculum focused on obtaining a detailed history, performing a complete neurological examination, and developing analytical skills to localize lesions. Students did learn about neuroimaging but training in EEG, which was often necessary for the diagnosis and management of epilepsy, was not routinely included. Based on our review we identified a need to develop a curriculum in EEG and epilepsy. We created an elective course in EEG and epilepsy at our center. This was a two-week rotation that was open to fourth-year students who had successfully completed their third-year neurology clerkship. During the course, students learned about different types of seizures, epilepsy syndromes and basic EEG studies. SMART (Specific, Measurable, Achievable, Result-Oriented, Time bound) goals were designed for evaluation. A minimum score of 3 on a 1-5 Likert scale was required to pass the course. Six students have completed this course so far and all students obtained a score >4. Five students entered neurology residencies and the sixth is a psychiatry resident.

Conclusions: Our pilot study indicates that there is a need to offer training in EEG and epilepsy for medical students, especially those interested in pursuing careers in neurology, neurosurgery and psychiatry. A structured curriculum with measurable goals and standardized grading is helpful.

573. Improving the Comfortability of Neurology Residents in Providing Care for Spanish-Speaking Monolingual Patients during Neurologic Emergencies

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Objective: To evaluate how a workshop teaching the focused neurologic exam in Spanish (FNES) affects the confidence of neurology residents in caring for Spanish-speaking monolingual (SSM) patients during neurologic emergencies

Background: An estimated 41 million U.S. residents, or 13.4% of the population, report speaking Spanish at home. During time-sensitive neurologic emergencies, interpreter services may be delayed or have limitations (i.e. low volume for phone/iPad interpreters). Studies have shown that patient safety and outcomes suffer when language barriers impede communication.

Design/Methods: A workshop was designed and implemented teaching the FNES to adult neurology residents at an academic, tertiary referral hospital. De-identified pre- and post-workshop surveys were distributed assessing past clinical experiences with SSM patients, confidence with the FNES, and comfortability managing SSM patients. Responses were collected using a mixture of Likert scale and numeric confidence scale. Data was analyzed using a paired t-test model.

Results: Fifteen neurology residents participated in the study. All participants reported managing a SSM patient during their training with fourteen of the fifteen reporting encounters with SSM patients during neurologic emergencies. Twenty percent either agreed or strongly agreed that interpretation services were readily available during neurologic emergencies. After the workshop, participants were significantly

more confident managing SSM patients during neurologic emergencies with and without the aid of an interpreter service (p=0.023, p=0.0002). Fourteen of the fifteen residents agreed or strongly agreed that their confidence in performing the FNES improved after the workshop.

Conclusion: After the workshop, neurology residents were significantly more confident in performing the FNES and more comfortable managing SSM patients. The skills provided during the workshop should be seen as an adjunct resource to available certified medical interpreters. Future studies assessing skill competency of residents after the workshop and the effect of a series of similar workshops on stroke management metrics in SSM patients (i.e. time to stroke interventions) would be helpful in assessing workshop effects.

574. Enhancing High Yield Resident Education in a High Volume Comprehensive Stroke Center Vascular Neurology Service

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Background: Neurology residents manage both clinical and educational demands, including being first responders to stroke codes. High yield resident education (HYRE) involves scheduled didactic sessions and morning report. Resident education can be compromised by high patient volume and acute patient care demands on Vascular Neurology services. At a comprehensive stroke center (CSC) located in the stroke belt of United States, stroke codes often occur during HYRE. To enhance the training and education of Neurology Residents, a Nurse Practitioner (ANP) was incorporated onto the Vascular Neurology service in 2018.The ANP manages stroke codes independently allowing for HYRE to be "protected time". The purpose of this study was to identify the number of stroke codes during HYRE in a single center CSC and assess the impact of APN managed stroke codes on HYRE time.

Method: We retrospectively reviewed all stroke codes from July 1, 2017 to June 30, 2018 and quantified the number of stroke codes that occurred during HYRE. The prospective work schedule of the ANP was analyzed on the retrospective data to assess how many stroke codes would have been managed by the APN during HYRE.

Results: We identified 18 hours per week of HYRE. A total of 1179 stroke codes occurred over a period of one year. 126 of these occurred during HYRE (10.68%). During HYRE, 107 of 126 (85%) stroke codes would have been independently managed by the ANP. HYRE would have been impacted in only 19 stroke codes (1.6%) when the APN was not available.

Conclusion: Neurology residency programs must maintain a balance between didactic, clinical, and practical educational requirements. The utilization of a Nurse Practitioner with full scope of practice can augment and protect HYRE while enhancing the overall education of Neurology Residents. The impact of the role of Advanced Practice Nurses and other Advanced Practice Clinical Professionals (e.g Physician Assistants) should be examined in all aspects of Vascular Neurology care and education.

575. Development of a Database Containing Detail Bedside Neurological Examination and Final Diagnosis

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Objective: Since bedside examination procedures for neuromuscular disorders has been developed in an age without CT / MRI imaging or other neuroimaging and neurophysiological examinations, it is important to make a new bedside diagnostic procedure based on recent neuro-imaging and neurophysiological diagnosis. So, we have developed a large neurological database for detail bedside neurological examination and evaluated each of techniques based on the statistical analysis.

Materials and Methods: We have established a corresponding database for the data of detail bedside neurological examination and its final diagnosis using an auxiliary diagnostic procedure. This database was created using FileMaker Pro software containing 5,208 fully neurologically examined cases. (3,438 cases of NHO Omuta hospital and 1,770 cases of Kochi medical hospital) These cases were finally diagnosed into 50 neuro-muscular disorders and each neurological technique were statistically evaluated by Chi-square test for the relationship between each findings and final diagnosis.

Results: Statistical analysis reveals,(1) Rossolimo reflex was examined in 1,440 patients, and 152 (10.6%) showed abnormalities. This reflex significantly appeared in patients with Parkinson-related diseases (PRD), frontotemporal lobe degeneration (FTLD), frontotemporal dementia (FTD) / ALS (FTD / ALS complex), and multiple cerebral infarction with dementia (DMCI) ($p < .05$)(2) Palmo-Mental reflex (PMR) was positive in 540 cases in 1,440 patients (12.4%), and 39 cases (0.9%) showed left-right laterality. Abnormal PMR significantly observed in Neuronal intranuclear inclusion disease (NIID), PRD and DMCI. ($p < .05$)(3) Abnormal abdominal skin reflex (ASR) (positive with laterality) was observed in 95 cases in 1,134 patients (8.38%). Statistically significant was observed in Cerebrovascular disease (CVD) ($p < .05$) and demyelinating disease such as MS or NMO ($p < .01$) and myelitis or myelopathy. ($p < .05$)

Conclusion: This database was developed on a commercially available software product. Setting up an outcomes database is straightforward and productive. Simple statistical analysis reveals several classical neurological reflex correlate with some neurological disorders. This database will improve the accuracy of bed-side neurological diagnosis and facilitate the use of neurological bed-side examination and provide the foundation for several clinical research studies.

329. Automated EEG Self-Indexing Research Repository and Data Core

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Electroencephalography (EEG) is commonly used to study seizures and, in the ICU, neurological status. With advances in machine learning, computational neuroscience and data science there is an increased interest in developing high-quality and comprehensive repositories of annotated, curated, intra- and extracranial EEG. The volume of data needed to apply computational techniques usually is large, but extracting data from proprietary systems can be prohibitively slow and cumbersome. Furthermore, classification of patient populations require separate clinical databases of imaging data, test results and queries of electronic medical record systems. In this study we describe a new EEG extraction pipeline that aims at reducing manual extraction of EEG from clinical systems. We describe the development of a series of software applications to allow the extraction of EEG data from clinical databases, bypassing clinical systems, and an automated indexing capability using clinical annotations produced by clinicians during routine clinical care. The next step employs a de-identify tool that removes patient identifiers from the EEG data and sends the data to a HIPPA compliant REDCap database that creates a unique identifier. The second component converts electrophysiologic data from proprietary formats and extracts clinical annotations. The third program uses annotations of the CSV files and indexes the data using an Elasticsearch webserver. With this pipeline it is possible to automate the entire process of transferring EEG in a clinical data repository to a useful and scalable research repository. This data is organized on a server that can run containerized applications for machine learning and other tasks. Furthermore, investigators are able to search the repository for EEGs of interest based on the clinical annotations generated during routine clinical care. In future work we will inter-connect each of the software components and develop a graphical user interface to facilitate search and use of the data repository by clinical researchers.

330. Patient Preferences for Treatment of Anxiety and Depression in an Adult Epilepsy Clinic

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Objective: While survey data suggests equipoise among epileptologists for managing anxiety and/or depression via prescribing in the epilepsy clinic versus psychiatry referral, patient treatment preferences are unknown. Thus, the primary objective of this study was to determine preference for anxiety and/or depression treatment by neurologists versus psychiatrists among a symptomatic epilepsy clinic sample.

Methods: Treatment preferences for anxiety and/or depression were surveyed in an adult tertiary care epilepsy clinic. Individuals who screened positive for anxiety and/or depression on validated instruments via a prospective, dual research and clinical screening protocol were recruited. Demographics, social variables, psychiatric treatment history, and treatment priorities and preferences were collected. Preference was defined as a slightly greater than 2:1 ratio in favor neurology or psychiatry; a two-sample binomial test assessed this primary objective. Multinomial logistic regression was conducted to assess an a priori multivariable model of treatment preference (secondary objective).

Results: The study sample included N=63 symptomatic adults, with 64% women and mean age 42.2 years. Most reported some past or current treatment for anxiety and/or depression, and treatment for these symptoms was a high or moderate priority among 65% of the sample. Neurologist medication management was preferred nearly 5:1 over psychiatry referral among those who chose neurology or psychiatry (as opposed to neither of the two; $p<0.0001$, 95% CI 0.702-0.919; 83% of 53). Multivariable modeling indicated preference for neither treatment (compared to neurologist management) was associated with low overall treatment prioritization and having never received neurologist medication management.

Conclusions: In this cross-sectional sample, patients indicated a strong preference for neurologists to manage anxiety and depression in the epilepsy clinic.

331. Marked Sleep Disruption in a Mouse Model of Medial Temporal Lobe Epilepsy

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In many patients with epilepsy, seizures have a predilection for a particular sleep-wake state or sleep-wake state transition. Further suggestive of a strong relationship between sleep-wake and seizures is the commonality of sleep disturbances in epilepsy and the improvement of seizures with the treatment of sleep disorders. While sleep-wake has been studied in patients with epilepsy, there are relatively few animal studies. We sought to examine the sleep effects of developing seizures in a mouse model of medial temporal lobe epilepsy. These studies will form the basis for cell-selective manipulations of sleep-wake networks to develop a mechanistic understanding of how sleep-wake circuits contribute to seizures. Mice were instrumented using a custom-designed head plate to permit reproducible recordings of the bilateral hippocampus, electrocorticogram, and electromyogram of neck muscles, with the later capacity for optogenetics and fiber photometry. Mice were habituated and underwent chronic video-EEG recording with intra-amygdala kainic acid microinjection by cannula one week later, and recording continuing for a further three weeks. Sleep was significantly disrupted: We found increased wake in mice with seizures (~ 15%, ANOVA $P = 0.019$) as

well as increased frequency ($P < 0.05$) and duration of seizures (ANOVA $P = 0.03$) during sleep in this model. Seizures were rarely observed in rapid eye movement (REM) sleep. These findings recapitulate observations from patients with MTLE and form a basis of further work that will cell-selectively manipulate components of sleep-wake networks to modify seizure risk and help understand underlying mechanisms.

332. Effects of Perampanel on Cognition & Quantitative Electroencephalography in Patients with Epilepsy

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Objectives: Antiepileptic drugs (AEDs) are well known for their effects on cognition and electrophysiologic changes. However, perampanel is yet to be evaluated for its effects on cognitive function and electroencephalography (EEG). The purpose of the present study was to identify the effect of perampanel on neuropsychological (NP) tests, quantitative EEG (QEEG), and its relationship with the blood level of the drug.

Methods: Seventeen patients with epilepsy were enrolled in the study. EEG recordings were obtained and NP tests were conducted before perampanel intake and 6 months after treatment. The relative frequency band power, peak alpha frequency, and NP test scores were compared before and after drug administration. The serum concentration of perampanel was correlated with the QEEG changes.

Results: Delayed recall of the Rey Complex Figure showed significant improvement (20.03 vs. 22.94; P=0.004) following perampanel administration. Other cognitive function tests showed no significant differences before and after drug administration. Theta frequency band power increased in all brain regions (P=0.001-0.03) and alpha frequency power decreased in the frontal and parietal regions (P=0.01 and P=0.02, respectively). The theta/alpha ratio, which represents background EEG slowing, increased in all brain areas (P=0.002-0.02). This increment of theta/alpha ratio in the central region positively correlated with the blood level of perampanel (r=0.5, P=0.05). The peak frequency of the alpha rhythm decreased after perampanel intake (t=2.45, P=0.03).

Significance: Perampanel induced electrophysiological slowing, but cognitive decline was not observed. Background EEG slowing correlated with the serum concentration of perampanel. Our results show the effect of perampanel on cognitive function and background EEG in adult patients with epilepsy for the first time.

333. Rolandic Epilepsy is a Risk for Delay in Development of Visuospatial Functions and Kinesthetic Praxis in Children

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Background: Benign epileptiform discharges of childhood (BEDC) is one of the most common forms of epilepsy in children. There are controversies about influences of this epilepsy on the neurocognitive abilities in children. Therefore it is necessary to do further researchers for clarifying this influence. The goal of this research was to reveal the effect of Rolandic epilepsy on neurocognitive abilities in children at the age of 7-8.

Methods: Experimental group included 21 children with Rolandic epilepsy (M = 7.45 years, SD = 0.75, 17 boys and 4 girls). The control group included 21 typically developing children. Children from experimental and control group were matched for gender and age. Children from both groups were assessed by Luria's neuropsychological assessment battery for children. Battery consists of 16 subtests which designed to assess 5 neurocognitive domains - visuospatial functions, memory, sensorimotor functions, language and executive abilities. One-way ANOVA was used for revealing group differences in the performance of subtests.

Results: We have revealed significant differences ($p \leq 0,05$) between groups for performance of 3 neuropsychological subtests which designed to asses visuospatial functions (Head subtest, Mental Rotation, Design Copying), and for performance of subtest for assessment of Kinesthetic Praxis. Children with Rolandic epilepsy performed these subtests worse in comparison to typically developing children.

Conclusion: In view of the obtained results it can be assumed that Rolandic epilepsy can cause the delay in the development of visuospatial abilities and kinesthetic praxis in children at the age of 7-8. However, we need to do further researcher for revealing the influence of Rolandic epilepsy on neurocognitive development of children. Particularly, we are going to do longitudinal investigation of children with this epilepsy one year later.

334. Rapid Dose Titration of Lacosamide: A Randomized, Multicenter, Prospective, Open-Label Study

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Purpose: Current guidelines for lacosamide dosing recommend a gradual titration with weekly dose escalation, which often necessitates long titration periods. However, a regimen of an initial loading dose of 200 mg followed by a maintenance dose of 200 mg/day is also used in practice, suggesting tolerability of more rapid titration schedules. We aimed to compare the safety and side effect profile of rapid titration protocols with reduced time interval compared to the conventional weekly dose titration.

Methods: We compared the safety of two rapid titration protocols to reach the target dose of 400 mg/day within 1 week along with the recommended weekly titration protocol (three weeks to reach 400 mg/day from 100 mg/day). The ≥50% responder rate and steady-state plasma concentration of lacosamide were also analyzed. Adverse events were assessed 1 week and 5 weeks after reaching target dose.

Results: Seventy-five patients with epilepsy were enrolled for three titration protocols, from which 5 patients were lost to follow-up and excluded from the safety analysis. Discontinuation of lacosamide or dose reductions due to adverse events occurred in 32 patients (46%), of whom a large majority (74%) had experienced adverse events after reaching 400 mg/day, demonstrating obvious dose-dependency. There was no difference in safety outcome among the three groups. Concomitant use of sodium channel blockers significantly increased the adverse events. However, the frequency of adverse events was not associated with titration protocol after adjustment for the use of sodium channel blockers.

Conclusions: The rapid titration protocols were not associated with an increased risk of adverse events compared to conventional titration protocol. Shortening the titration interval with appropriate target dosage may be feasible in appropriate clinical situations.

335. Usefulness of Saliva for the Therapeutic Drug Monitoring of Perampanel

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Objective: Therapeutic drug monitoring (TDM) of antiepileptic drugs (AEDs) helps optimize drug management for patients with epilepsy. Salivary testing is noninvasive and easy, with several other advantages. Owing to technical advances, salivary TDM has become feasible for several drugs, including AEDs, and its value has been investigated. Until recently, saliva TDM had not been studied for perampanel (PER). The purpose of our study was to confirm whether saliva is a biological substitute for blood in PER TDM.

Methods: Adult patients diagnosed with epilepsy prescribed PER from August 2018 to March 2019 at Seoul National University Hospital were enrolled. Total and free PER were measured in simultaneously obtained plasma and saliva samples using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and high-performance liquid chromatographic (HPLC). We examined the correlations between saliva and plasma PER concentrations and whether the use of concomitant medications classified as cytochrome P450 (CYP) 3A4 inducers affected the correlations.

Results: Thirty patients were enrolled, aged 16 to 60; 10 (33%) were women. Patients were on 2 to 12 mg (mean, 6 mg) of PER. The average total and free concentrations of PER were 343.02 (46.6-818.0) ng/ml and 1.53 (0.51-2.92) ng/ml in plasma and 9.74 (2.21-33) ng/ml and 2.83 (1.01-6.8) ng/ml in saliva, respectively. There was a close linear relationship between the total PER concentrations in plasma and saliva as well as the free form. (both $p < 0.001$; $r= 0.678$ and 0.710, respectively). The change in the PER concentration caused by CYP3A4 inducer did not affect the correlation between saliva and plasma concentrations. (all $p < 0.001$).

Significance: The PER concentration in saliva was correlated with that in plasma. This correlation was not decreased by CYP3A4 inducers. Our results demonstrate for the first time that PER is measurable in saliva and that this matrix has therapeutic potential for PER TDM

336. Trends in Oral Anticoagulant Co-Prescription with Valproic Acid among Adults with Epilepsy, 2010-2018

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Background: Prior research has suggested that the pharmacokinetics of warfarin, and potentially direct oral anticoagulants (DOACs), may be substantially impacted by concurrent use of valproic acid. To understand the clinical implications of proposed interactions and guide future research, we sought to quantify the prevalence and assess the patterns of co-prescribing of oral anticoagulants (OACs) with valproic acid among adults with epilepsy.

Methods: We conducted a retrospective assessment of OAC and valproic acid prescription fills using the 2010-2018 OptumInsight Clinformatics™ Data Mart, a large US commercial and Medicare Advantage health insurance claims database. Included enrollees were >18 years old with ICD-9/10 codes for epilepsy. Prescription fills lasting >14 contiguous days were counted annually for valproic acid, as well as for lacosamide, lamotrigine, and levetiracetam, which have similar clinical indications, but no anticipated interactions with OACs. The annual prevalence of overlapping prescription fills (>14 days) for OACs were calculated over successive years, and monotonic temporal trends were assessed using the Spearman rank correlation coefficient. Multivariable logistic regression models were built to evaluate the associations of sociodemographic characteristics with concomitant prescribing patterns. Missing values were imputed with multiple imputation by chained equations.

Results: Among adults with epilepsy, the prevalence (per thousand) of concurrent valproic acid and OAC use increased from 51.7 in 2010 to 94.0 in 2018 (OR 1.90, 95%CI 1.43-2.55; P<0.001). From 2010 to 2018, the yearly % change in DOAC co-prescribing with valproic acid was continuously positive: +0.31, +0.22, +0.74, +0.84, +0.85, +0.48, +1.92, +1.16 (Spearman's rho=1.00; $P < 0.001$); contrasting, the yearly change in warfarin co-prescribing: +0.75, +1.15, -0.84, -0.56, -0.80. +0.01, -1.10, -0.57 (Spearman's rho= -0.77; P=0.016). By 2018, apixaban and rivaroxaban had significantly surpassed dabigatran in terms of co-prescribing with valproic acid, with prevalence (per thousand) of 39.2,

24.1, and 1.9, respectively. In multivariable analysis of OAC use in 2018, age, gender, sex, race, education level, and net worth were not associated with dispensing of valproic acid versus the non-interacting, comparator antiepileptic drugs. However, regional differences between groups were observed, with those dispensed valproic acid more likely to be in the Mid-Atlantic U.S.

Conclusions: Concomitant prescribing of OACs has risen to 9.4% among adults with epilepsy on valproic acid. These findings reveal the high clinical relevance, and ensuant critical need for further investigation into these drug combinations, particularly focusing on valproic acid prescribing with factor Xa inhibitors.

337. HLAs Associated with Perampanel-Induced Psychiatric Adverse Effects in a Korean Population

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Objective: Perampanel (PER) is a new-generation antiepileptic drug that has an occasional but significant shortcoming, psychiatric adverse effects (PAEs). Recently, antiepileptic drug-related adverse reactions, such as skin rash and even PAEs, have been discovered to be correlated with certain human leukocyte antigen (HLA) types. Thus, we aimed to analyze specific HLA alleles as risk factors for PER-PAEs.

Methods: We prospectively enrolled 17 patients with epilepsy who were prescribed PER between May 2016 and Jul 2018 at Seoul National University Hospital and developed PAEs while taking PER. Their HLA types were analyzed compared to those of 19 patients in the PAE-tolerant group and the general Korean population. *In silico* docking was performed with two different computational programs, AutoDock Vina and SwissDock, to theoretically evaluate the binding affinity of PER in the grooves of the specific HLA alleles.

Results: The HLA-DQB1*06:01, DRB1*08:03, and B*54:01 alleles were significantly associated with the patients who developed PER-PAEs compared with the general Korean population (odds ratio [OR] 3.94, p=0.008, OR 9.24, p=0.037, and OR 3.25, p=0.041, respectively). As a haplotype, the combination of the three alleles was significantly more frequent in the PER-PAE group than in both the PER-tolerant group and the general Korean population. DQB1*06:01 and B*54:01 also demonstrated higher docking scores with PER than other alleles.

Conclusions: This is the first study to analyze the association of PER-PAEs with specific HLA genotypes. Our results suggest that an HLA-associated genetic predisposition and a possible immunological mechanism are involved in the occurrence of PER-PAEs.

338. A New Rapid Titration Protocol for Lamotrigine That Reduces the Risk of Skin Rash

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Objective: Lamotrigine is one of the most widely used antiepileptic drugs, but it has a critical issue of a skin rash if the starting dose is too high or the escalation rate is too rapid. We investigated the efficacy and safety of a novel and rapid titration protocol for lamotrigine that takes only 11 days to reach a daily dose of 200 mg.

Methods: We prospectively enrolled 33 adult patients (age 18-85) who were diagnosed with epilepsy and started lamotrigine administration for the first time at a single tertiary hospital. Our new protocol starts with a subthreshold dose of the drug and then administer a stepwise-incremental dose until reaching the full therapeutic dose within 11 days.

Results: Of 29 patients analyzed, only two (6.9%) experienced idiosyncratic skin rash before the first follow-up visit at 2 weeks (±3 days). In addition, a therapeutic concentration was reached in more than 75% of studied patients after 2 weeks of lamotrigine administration.

Conclusions: These findings demonstrate the value of the novel tolerance induction protocol for lamotrigine, which could widen the available application of lamotrigine in various situations.

339. Pharmacokinetic Analysis of Oxcarbazepine and Its Metabolite Mono-Hydroxylated Derivative in Patients with Epilepsy

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Objective: Oxcarbazepine is a widely used anticonvulsant drug to treat focal seizure as monotherapy or adjunctive therapy. The mono-hydroxylated derivative (MHD) is the main metabolite which is responsible for most of the anticonvulsant activity. The objectives of this study are to develop a pharmacokinetic model of oxcarbazepine and to analyse the relationship between trough concentrations of the drug and occurrence of adverse event (AE) or seizure.

Methods: To develop a pharmacokinetic model of oxcarbazepine, the data from two studies were used; the data of 447 patients who had been enrolled in from Epilepsy Registry Cohort of Seoul National University Hospital since Feb 2011 and the data of pharmacokinetic study involving 40 patients evaluating oral loading of oxcarbazepine. Plasma concentrations of MHD were analysed using nonlinear mixed-effect modelling in NONMEM (ver 7.3). The first-order conditional estimation with interaction method was used to fit the plasma concentration-time data. Trough concentrations of each patient were calculated using the final pharmacokinetic model. The relation between trough concentrations and occurrence of AE or seizure were analysed using Students' t-test.

Results: A one-compartment model with first-order absorption, and a proportional error model describes oxcarbazepine pharmacokinetics adequately. The body weight was significant covariate for the clearance and the volume of distribution of the drug and the use of concomitant drugs including carbamazepine, phenytoin, and phenobarbital which are known to be enzyme-inducers increased the clearance 1.38-fold. The trough concentrations of the drug were slightly higher in the patients group with AEs (mean ± SD; 13.4 ± 7.8 ng/mL) or with seizure episodes more than once (13.9 ± 7.6 ng/mL) compared to the non-AE group (12.4 ± 6.8 ng/mL) or non-seizure group (12.7 ± 7.2 ng/mL) but the differences were not statistically significant.

Conclusions: The population pharmacokinetic model developed in this study adequately described oxcarbazepine pharmacokinetics in patients with epilepsy. The covariates selected in this study including body weight and the use of concomitant drug are expected to be used to choose appropriate dosage regimen in the patients.

340. Perampanel in Patients with a History of Psychiatric Illness: Post Hoc Analysis of Four Randomized Phase III Studies (304, 305, 306, and 335) and Their Open-Label Extensions (307 and 335 OLEx)

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Purpose: Dose-dependent psychiatric and behavioral treatment-emergent adverse events (TEAEs) have been reported with perampanel, and dose reduction is advised if these symptoms occur. This post hoc analysis assesses psychiatric safety data from four randomized controlled trials (RCTs) of perampanel (Studies 304/305/306/335) and their OLEx Phases (Studies 307/335 OLEx) in patients with focal epilepsy with or without a history of psychiatric events.

Methods: TEAEs were analyzed for patients with or without a history of psychiatric events. In RCTs, patients were pooled by actual perampanel dose and compared with pooled placebo. All OLEx patients received perampanel.

Results: In RCTs, 352 (16.1%) patients had a psychiatric history (perampanel n=244; placebo n=108); 1835 (83.9%) patients had no psychiatric history (perampanel n=1325; placebo n=510). The frequency of TEAEs and psychiatric TEAEs depended on perampanel dose. In patients with a psychiatric history, psychiatric TEAEs occurred in 73 (29.9%) and 21 (19.4%) patients with perampanel and placebo, respectively. With perampanel 2 and 4 mg/day, psychiatric TEAEs were less frequent than placebo (11.1% and 15.4% vs 19.4%, respectively). The most common psychiatric TEAEs with perampanel in patients with a psychiatric history were anxiety (5.3%) and insomnia (4.9%). In patients without psychiatric history, psychiatric TEAEs occurred in 157 (11.8%) and 47 (9.2%) patients with perampanel and placebo, respectively. Psychiatric TEAEs were more frequent in patients with a psychiatric history for all combined doses (P<0.01) and placebo (P<0.01). The most common psychiatric TEAEs with perampanel in patients without a psychiatric history were insomnia (2.0%), aggression (2.0%), and anxiety (1.8%). In OLEx Phases, 283/1895 (14.9%) patients had a psychiatric history. Psychiatric TEAEs occurred in 151 (53.4%) and 521 (32.3%) patients with or without a psychiatric history, respectively (P<0.01). The most common psychiatric TEAE was irritability (16.3% and 10.4% in patients with or without a psychiatric history, respectively).

Conclusion: Psychiatric TEAEs are reported by more patients with a psychiatric history than without, and were dependent on perampanel dose irrespective of previous psychiatric illness. In patients with or without psychiatric history, perampanel 2 and 4 mg/day did not increase psychiatric TEAE incidence compared with placebo.

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341. Microgrid Recordings from the Human Hippocampal Surface *In Vivo* Reveal Multidirectional Traveling Waves

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Background: The human hippocampus has diverse topographic interconnections with other brain regions at either end (septal and temporal poles). These hippocampal-cortical systems support memory and other cognitive functions, which are commonly affected in neurological diseases. How this mix of neural information is flexibly integrated across the hippocampus is unclear however, since cycles of theta frequency activity (4-10 Hz) are believed to propagate only unidirectionally toward the temporal pole. Direct electrophysiological recordings in vivo rely on penetrating depth electrodes due the secluded deep-brain location, but this sparse sampling has undermined the study of spatiotemporal oscillation features that may be crucial for hippocampal processing.

Methods: To address this challenge, we recorded from novel thin-film microgrid arrays (8x4 layout, 2mm spacing) conformed to the human hippocampal surface in six participants undergoing temporal lobe surgery. This allowed us to examine spectral profiles of distinct electrophysiological oscillations in high spatial resolution over the CA1 subregion. We also applied 2-D plane wave regression to oscillation phases to understand whether hippocampal oscillations flow across the hippocampus in other versatile ways that otherwise cannot be observed or accurately measured using depth electrodes (e.g. exact angle, wavelength, and speed). We additionally sought to clarify whether wave propagation extends to other low frequencies in delta (1-4 Hz) and alpha (10-15 Hz) ranges, since they may herald distinct cortico-hippocampal communications.

Results: Oscillations in the delta, theta, and alpha bands all traveled across the hippocampal surface obliquely with both longitudinal and transverse components, and this

directionality that was mirrored between the hemispheres. Moreover, the travel routes of nearly all detected frequencies dynamically changed throughout the recording, usually by reversing or following other prevalent angles along a predominant propagation axis. These tendencies were predicted by oscillation amplitude patterns across the grid suggesting differential circuit engagement. Lastly, two participants were awake and performed a visual naming task which modulated traveling oscillations.

Conclusions: Low-frequency oscillations appear to propagate in multiple directions over the human hippocampal surface, and their instantaneous directions may represent novel biomarkers of distinct meso-scale network computations. Broadening from a unidirectional to a multidirectional propagation interpretation may shed light on mechanistic theories of hippocampal-dependent cognition including the timing of phase-encoded neural firing and hierarchical cognitive/memory processing. We speculate that future studies delineating the specific circuits that drive wave propagation routes could also yield targetable patterns for therapeutic neuromodulation.

342. Seizure Prevalence in Autoimmune Encephalitis- A Systematic Review

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Purpose: Autoimmune encephalitis (AE) refers to a group of neuroinflammatory diseases caused by autoantibodies against various neuronal receptors or cell surface proteins that may result in a broad range of symptoms, including seizures, cognitive deficits, and psychiatric symptoms. Presentation can vary widely by autoantibody, and understanding of the full clinical spectrum of AE continues to evolve. To elucidate the burden of seizures in this population, this study aimed to evaluate the prevalence of seizures and electroencephalogram (EEG) abnormalities in AE and its most common subtypes.

Methods: PRISMA standards were followed for this systematic review, and the protocol was registered with PROSPERO. We searched PubMed, Embase, and PsychINFO from inception to June 1, 2019 for articles pertaining to AE and seizure. All steps were performed in duplicate. Studies were included if they reported seizure and/or EEG data in cohorts of $\geq$10 AE patients. Extracted data included patient demographics, antibody type, seizure incidence, and EEG findings. In addition to descriptive analysis, stratified analysis by autoantibody subtype were performed with ANOVA and Chi-square analyses.

Results: Of the 3,863 abstracts reviewed, 1,616 were selected for full text review, and 124 studies met eligibility criteria. These studies included data from 3,186 individual AE patients, of whom 2,313 (72.6%) had clinical seizures during the course of their illness. There were 1,960 patients (61.5%) with anti-NMDA receptor encephalitis (anti-NMDARE), the most common AE subtype, of whom 1,428 (72.9%) had clinical seizures during their illness. The second most common AE subtype was anti-LGI1 encephalitis, which included 550 patients, 445 (80.9%) of whom had clinical seizures during their illness. Seizures were more common in younger patients, particularly those 13-17 years old, both for all AE patients ($p<0.05$) and in those with anti-NMDARE ($p<0.01$). There was no statistically significant difference identified in seizure prevalence between sexes. Of the 1,995 patients with AE who had EEG data available, 1,765 (88.5%) had some EEG abnormality (e.g., epileptiform discharges, slowing, etc.). This included 1,230/1,330 (92.5%) of the patients with anti-NMDARE and 319/365 (87.4%) of the patients with anti-LGI1 encephalitis.

Conclusions: Results of this systematic review provide an estimate of the prevalence of seizures in AE, confirming the magnitude of seizure burden in this population. Prospective studies are needed to identify factors associated with seizures and to evaluate the role of particular EEG findings as biomarkers of seizures and outcomes in AE.

343. Tranexamic Acid and Post-Operative Seizures: The Glycine Connection

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Objective: To report a case of post-operative seizure following intraoperative tranexamic acid (TXA) administration and discuss the molecular mechanism behind the association.

Background: TXA is an antifibrinolytic drug routinely used to reduce postoperative blood loss and transfusion requirements during surgery.[1] However, TXA has been shown to increase the risk of post-operative seizures, most noted after cardiac procedures but also seen in nonsurgical patients.[1]

Design/Methods: Case Report

Results: A 79-year-old female with a past medical history of coronary artery disease, atrial fibrillation, and an L3-L5 posterior decompression 7 years prior presented for severe and worsening lower back and lower extremity pain and was admitted for lumbosacral stabilization surgery. During the procedure, she received a total of 1.4 g of TXA. In the immediate post-operative period, she developed clinical seizure-like activity described as facial twitching and left arm movement. While undergoing a Computed Tomography (CT) imaging of the head, she had another episode of seizure-like activity with facial twitching and flexor posturing lasting for 2 minutes. She was intubated and transferred to the intensive care unit (ICU) where a 3rd episode of seizure-like activity occurred. She was started on multiple anticonvulsants at this point. CT Head and CT angiogram head & neck were unremarkable. Spot EEG showed no electrographic seizures. Due to lack of conclusive seizure history, it was inferred that current seizure-like activity was due to TXA received intraoperatively.

Discussion: In animal trials examining the mechanism behind the TXA and seizure association, application of TXA to slices of neocortex showed an increased frequency of spontaneous epileptiform field potentials revealing that TXA

directly increased excitability of neuronal networks.[1] Glycine is structurally similar to TXA, and glycine receptor antagonists such as strychnine cause a similar pattern of movements to the seizures observed in patients treated with TXA.[1] Application of TXA to cortical neurons and plotting results on concentration-response curves shows that TXA acts as a competitive antagonist at glycine receptors.[1] Several general anesthetics (e.g. isoflurane and propofol) act as positive allosteric modulators of glycine receptors and might be effective in the treatment of TXA-associated seizures by prolonging the delivery during the early postoperative period.[1]

Conclusion: The risk of seizures is increased in patients with TXA exposure intraoperatively and this likely results from the drug acting as a competitive antagonist at glycine receptors.

References: 1. Lecker I. Tranexamic acid-associated seizures: causes and treatment. Ann Neurol. 2016

344. STAT3 Inhibition Reduces Seizure Frequency and Cognitive Co-Morbidities in a Mouse Model of Temporal Lobe Epilepsy

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Temporal lobe epilepsy (TLE) often develops after a brain insult activates ongoing molecular cascades and neural circuit remodeling in the hippocampus resulting in increased susceptibility to spontaneous seizures and cognitive dysfunction. Targeting these cascades after a brain injury and/or in TLE patients could prevent or reverse their symptoms and have the potential to provide a viable disease-modifying treatment, especially for the over 30% of TLE patients who do not respond to currently available treatments. In recent years, the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway has been implicated in the pathogenesis of TLE. The JAK/STAT pathway is known to be involved in inflammation and immunity, and only more recently has been shown to be associated with neuronal functions such as synaptic plasticity. Our laboratories previously showed that a JAK inhibitor, WP1066, could greatly reduce the number of spontaneous seizures that animals went on to develop in the rat pilocarpine model of status epilepticus (SE). We have continued to investigate the mechanism of JAK/STAT-induced epileptogenic responses through the use of a new mouse transgenic line we developed where STAT3 knockdown (KD) can be controlled by tamoxifen-induced CRE expression specifically in forebrain excitatory neurons via the Calcium/Calmodulin Dependent Protein Kinase II alpha (CamK2a) promoter. We now report that this knockdown of STAT3 (nSTAT3KD) markedly reduces spontaneous seizure frequency in the intrahippocampal kainate model (IHKA) of TLE and ameliorates IHKA-induced memory deficits as measured by Contextual Fear Conditioning. Recently, using deep RNA-sequencing, we also discovered transcriptomic signatures 24 hours after SE that occur in response to IHKA injections (ipsilateral and contralateral to the injection site) and are in part reversed by nSTAT3KD. The emerging transcriptome for STAT3 in the context of temporal lobe epilepsy suggests that it may be useful for identifying potential epileptogenic gene networks that were previously unknown and identifying potential new targets for the treatment of intractable epilepsies.

345. A Prospective, Longitudinal, Observational Study of the Natural History and Functional Status of Patients with Lafora Disease

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Lafora disease (LD) is a rare, fatal autosomal recessive neurodegenerative disorder caused by loss of function mutations in either the *EPM2A* or the *EPM2B* gene which encode laforin and malin, respectively. Mutations result in over-activation of glycogen synthase leading to excess production and intracellular accumulation of glycogen and polyglucosan, an aberrantly branched and insoluble form of glycogen. The earliest signs of Lafora disease, presenting in late childhood or early adolescence, are generally visual hallucinations, absence seizures, facial myoclonus rapidly progressing to generalized myoclonic activity and generalized seizures followed by ataxia, severe cognitive decline and dementia. Death typically results as a complication of status epilepticus about 10 years after disease onset. Therapy involves antiepileptic medication, which may reduce seizure frequency and severity initially, but does not prevent disease progression. Other therapeutic measures are supportive in nature. Published reports on LD include single center retrospective chart reviews. However, no prospective multi-center study using clinical scales, questionnaires or biomarkers has been conducted, to date. We have enrolled over 30 Lafora disease patients in a 2-year prospective, longitudinal observational study at 4 US and European sites to better characterize and quantify changes in functional status and biomarkers over time. Eligibility criteria include genetically confirmed diagnosis of Lafora disease, age >5 years and sufficient functional ability to perform neuropsychological testing. Assessments, performed every 6 to 12 months, include seizure frequency and characterization (diary and 24-hour video EEG) and measures of intelligence (Leiter), cognitive function (Woodcock-Johnson, Children's orientation and amnesia test and Colors Trails test, Beery Buktenica Developmental

test of Visual Motor Integration, Rey Complex Figure test), ataxia (Scale for Assessment and Rating of Ataxia), disability (PEDI-CAT), motor function (6 Minute Walk Test, gait analysis, timed functional tests) and quality of life (QOLIE). In addition, a disease-specific composite Lafora Disease Clinical Performance Scale comprising 6 domains (LDCPS; total 0-18 points) is being administered and serum and cerebrospinal fluid are being obtained for biomarkers. Baseline data will be presented.

346. Late Perampanel Treatment Stops Severe Midazolam-Refractory Status Epilepticus

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Objective: To assess the effectiveness of perampanel, a specific antagonist for AMPA-type glutamate receptors, as a second-line treatment of benzodiazepine-unresponsive status epilepticus (*SE*).

Background: *SE* responds poorly to benzodiazepines when treatment is delayed. Pathophysiological studies show that *SE* causes an early maladaptive internalization of synaptic $GABA_A$ receptors, which causes benzodiazepine pharmacoresistance, along with a migration of NMDA and AMPA receptors (AMPAR) towards synapses, which increases glutamatergic excitation. Topiramate, an AMPAR antagonist, is effective in refractory *SE*. The stronger AMPAR antagonist perampanel is active in a standard model of SE (Hanada et al Pharmacol Res Perspect 2014) and deserves evaluation as a second-line drug in the late treatment of severe, benzodiazepine-refractory *SE*.

Design/Methods: *SE* was induced in adult male Sprague-Dawley rats by high-dose lithium (5 mEq/kg)/pilocarpine (320 mg/kg), and EEG/video was recorded for 18 hrs. Midazolam (1 mg/kg) was injected i.p. 40 min after SE onset. Perampanel (0.5, 1 or 2 mg/kg), valproate (270 mg/kg), levetiracetam (240 mg/kg), fosphenytoin (120 mg/kg PE) or lacosamide (24 mg/kg) were injected i.p. 60 min. after seizure onset (20 min after midazolam) if *SE* continued.

Results: Perampanel 2 mg/kg reduced the time needed for EEG amplitude to decline to twice the pre-seizure baseline (median 8 min; interquartile range: 6 min - 26 min), compared to midazolam (47 min; 32-172 min; $p < 0.05$), suggesting earlier *SE* termination, while valproate, levetiracetam, fosphenytoin or lacosamide failed to achieve a significant reduction of that time. Perampanel (2 mg/kg) reduced EEG power integral (EEGPI) during the first hour after treatment to a value below the pre-seizure baseline, demonstrating that seizures were terminated (mean $\pm$ SE -101 $\pm$80; $p<0.0001$ compared to midazolam alone). Valproate, levetiracetam and lacosamide did not reduce EEGPI significantly and fosphenytoin reduced it mildly (238 $\pm$139, $p<0.01$) compared to midazolam alone. After perampanel, EEGPI remained below the pre-seizure baseline at 2, 4 and 6 hours, (all $p<0.0001$ compared to midazolam), documenting the lack of seizure recurrence, which is a common occurrence. Neither valproate, levetiracetam, fosphenytoin nor lacosamide reduced EEGPI below the pre-seizure baseline at 2, 4 or 6 hours.

Conclusion: Perampanel is potent in stopping midazolam-refractory *SE* even when given 60 min following *SE* onset. Used as a late second-line treatment, perampanel is more effective in terminating SE than valproate, levetiracetam, fosphenytoin or lacosamide in this animal model of severe benzodiazepine-refractory *SE*.

347. Caregiver Burden in Psychogenic Non-Epileptic Seizures

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Objective: Caregiver burden in psychogenic non-epileptic seizures (PNES) is an important but understudied reality. The objective of this exploratory study was to quantify caregiver burden in PNES and identify the relative contributions of patient and caregiver related characteristics to it.

Methods: PNES patients and caregivers completed surveys about demographic, disease related and psychosocial characteristics during their Epilepsy Monitoring Unit (EMU) admission. Associations were evaluated using the Zarit Caregiver Burden Inventory (ZCBI) score as an independent variable and the patient and caregiver related characteristics as dependent variables.

Results: 43 patients and 28 caregivers were recruited. The majority of patients were on average 36 years old, single women, unemployed, with some college education. The majority had PNES for 8 years averaging 20 seizures per month and were previously maintained on ≥ 2 antiseizure medications. Most caregivers were first degree relatives with a mean age of 43 years, married employed women of higher educational attainment, typically cohabitating with the patients. Caregiver burden was within the mild-moderate range (ZCBI mean score 28). That burden appeared higher in unemployed caregivers of male patients. In the univariate analysis, patient quality of life, depression and anxiety, and medication side effects, as well as caregiver stigma, depression and anxiety emerged as potential contributors, with patient quality of life and caregiver depression standing out as statistically significant factors in the multivariate regression analysis.

Conclusion: There is substantial caregiver burden in PNES. It is associated with both the patient and the caregiver psychosocial well-being in a reciprocal relationship.

348. A Rare Case of Autonomic Epilepsy

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Background: Autonomic seizures are focal non-motor seizures that primarily affect the central autonomic network.

Objective: The aim of this review is to provide a descriptive review of Autoimmune epilepsy with more focus on the

clinical aspects of the condition; along with an illustrative case report.

Illustrative Case Report: A 71-year-old female, with a past medical history of hypertension presented to the clinic with episodes of 'syncope' that began 24 years ago, following a concussion from a motor vehicle collision. Though the frequency of her spells had increased over the past 15 years, it almost always occurred in the middle of the night and are stereotypical. Each spell begins with a feeling of hot sensation, nausea, and the urge to have a bowel movement. On getting out of bed, she feels dizzy and sweats excessively which she described as 'drenching'. She vomits or has a bowel movement then wakes up on the bathroom floor with no recollection of what happened. On regaining consciousness, she feels dizzy but makes it to her bed, falls asleep, and feels tired throughout the following day. Her last spell was witnessed by her daughter, on an afternoon and the whole episode lasted 2-5 minutes, associated with bladder incontinence. Her neurological examination was unremarkable and workup including extended 1-hour video EEG was normal. Magnetic Resonance Imaging (MRI) of the brain without contrast showed bilateral parenchymal volume loss within the hippocampi and mesial temporal lobes with prominent temporal horns. She was diagnosed with autonomic epilepsy and treated conservatively with oral levetiracetam.

Review Method: A literature search was done on PubMed using the keyword 'Autonomic Seizures'. Studies in the English language literature were descriptively analyzed for our review.

Review Results: 1. The International League Against Epilepsy 2017 classified autonomic seizures as non-motor focal seizures. 2. Manifestations- changes in blood pressure, heart rate; gastrointestinal and respiratory symptoms; pallor, flushing, piloerection, and sweating; urinary symptoms; sexual auras, and sexual automatisms. 3. Diagnosis is clinical and evidence-based guidelines for management are unavailable. 4. Epilepsy surgery is recommended in cases with uncontrolled seizures. 5. Seizure control is imperative to prevent sudden unexplained death.

Conclusion: Autonomic epilepsy is diagnosed when the primary manifestation is autonomic symptoms with or without impairment of consciousness. Recognition is key, antiepileptic medications are effective and seizure control is important to prevent complications like sudden unexplained death.

349. Children and Adolescents with Idiopathic Generalized Epilepsy Treated by AEDs: Changes in Speech Development

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Background: The influence of antiepileptic drugs (AEDs) on speech development in children and adolescents (C&A) is more precisely assessed in idiopathic generalized epilepsy (IGE) which affects cognitive functions (CF) minimally. The information on valproic acid (VA) effectiveness and side effects is actively discussed; however, data on changes in CF and speech in C&A are fragmentary.

Aim: To evaluate changes in verbal thinking productivity of C&A with IGE treated by VA.

Methods: We examined 66 C&A from 6 to 18 years. The study group (SG) included 23 C&A with IGE. 13 C&A were excluded (6 C&A received polytherapy; 7 C&A had cognitive deficit before IGE onset). 30 C&A (neurologically healthy children of the corresponding age with normotypic cognitive development) formed the control group (CG). In 2018 the authors worked out Russian-language neuropsychological battery for the assessment of CF in C&A treated by AEDs. Speech was assessed by this battery before treatment, after 3, 6, 9, 12, 18 months in SG, at the same intervals in CG. Relative risk scores for adverse outcomes and their 95% confidence interval were calculated using Revman 5.3. The number of C&A with misunderstanding of phraseological units (PU-test) and C&A making mistakes in odd-one-out tasks (OOO-test) were considered as an unfavorable outcome. The obtained data were compared for the SG and the CG (the results were considered significant at $p<0.05$).

Results: Comparative analysis of PU-test results: before treatment, after 3 months RR=1.04; 95% CI [0.27, 4.30]; after 6 months RR=1.30; 95% CI [0.43, 3.97], after 9, 12 months RR=1.96; 95% CI [0.62, 6.13], after 18 months RR=4.29; 95% CI [1.31, 13.97]. Comparative analysis of OOO-test results: before treatment RR=1.04; 95% CI [0.32, 3.46]; after 3 months RR=1.30; 95% CI [0.43, 3.97]; after 3, 6 months RR=1.96; 95% CI [0.62, 6.13]; after 12 months RR=2.61; 95% CI [0.89, 7.61]; after 18 months RR=3.91; 95% CI [1.19, 12.84]. Statistically significant decrease in productivity of verbal thinking was registered in the study group after 18 months (p=0.02).

Conclusion: VA influences negatively the productivity of verbal thinking: statistically significant decrease is registered after 18 months after the start of treatment. The results show that epileptologists should control the development of cognitive functions, especially speech, in children treated by VA. The reported study was funded by Russian Foundation for Basic Research (RFBR) according to the research project 17-29-09096.

350. The Effect of Human Herpes Virus 6 on Hippocampal Volumes in Temporal Lobe Epilepsy

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The most common pathology in mesial temporal lobe epilepsy (MTLE), one of the most common drug-resistant epilepsy syndromes, is mesial temporal sclerosis (MTS), characterized by focal gliosis and neuronal loss. Several studies have found evidence for persistent human herpes virus 6 (HHV-6) replication in resections from MTLE/MTS patients. To study the viri's potential role we investigated patterns of hippocampal volume loss in a prospective case series of 41 patients (19 men) who had temporal lobectomy

and measurement of HHV-6 in resected hippocampal tissue. Mean age of seizure onset, age at surgery, and presurgical epilepsy duration were 10.07, 35.03, and 24.96 years respectively. Viral DNA was detected via real-time and digital droplet PCR. We used Freesufer 6.0 to quantify hippocampal volumes. SPSS was then used to compare volumes between patients with and without evidence for persistent HHV-6 viral DNA replication in resected surgical specimens. Statistical analyses using SPSS included Student's T-test for independent sample means and analysis of variance. Significance was set at $p<0.05$.We observed 22 HHV-6 positive and 19 negative patients. Mean hippocampal volume ipsilateral to the seizure focus was lower in those without HHV-6 than with HHV6 (2618.21 vs. 3122.80, p=0.01). ipsilateral/contralateral ratios for whole hippocampal and subfield volumes for HHV-6 negative were uniformly lower than for HHV-6 positive patients (p=0.02). Pre-surgical epilepsy duration was 29.53 for HHV6-negative and 21.36 for HHV-6 positive patients (p=0.02). However, in multivariate analysis only HHV-6 status had a significant effect on hippocampal volume. Our data suggest multiple potential etiologies for MTS. HHV-6 negative hippocampi had significantly greater preoperative atrophy than hippocampi positive for virus. HHHV-6 may have a less severe effect on hippocampus than other etiologies.

351. The Referential Montage Poorly Localizes Cortico-Cortical Evoked Potentials

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Introduction: Cortico-cortical evoked potentials (CCEPs), resulting from single pulse electrical stimulation, are increasingly being used to understand seizure networks, as well as normal brain connectivity. However, we observed that when using depth electrodes, traditional measures of CCEPs amplitude using a referential montage are falsely localizing, often to white matter.

Methods: We pooled 22 linear electrode arrays targeting the amygdala or hippocampus from eight patients. We classified contacts in being in gray matter, white matter or bordering each, and measured the amplitude using the root-mean squared (RMS) deviation from baseline in either a referential, bipolar or Laplacian montage.

Results: 21/22 (95%) electrode contacts had a significantly higher mean amplitude when in gray matter than in white matter using a Laplacian montage, which was significantly more than the 10/22 (45%) electrodes when using a referential montage (p=0.0006, Fisher exact test). The area under the curve for a receiver operating characteristic classifying contacts as gray or white matter was significantly higher for the Laplacian (0.87) or the bipolar montage (0.83) when compared to the referential montage (0.56) ($p < 0.001$, boot-strap).

Conclusions: Both the Laplacian and bipolar montage were superior to a referential montage in localizing CCEPs to gray matter. These montages may be more appropriate for interpreting CCEPs when using depth electrodes than the referential montage, which has typically been used in studies of CCEPs.

352. An Approach to the Analysis and Successful Treatment of Epilepsy Due to Periventricular Nodular Heterotopia - Corticocortical Evoked Potentials, Signal Processing and Radiofrequency Ablation

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Periventricular nodular heterotopia (PVNH) is a common malformation of cortical development that often causes refractory focal epilepsy. Stereoelectroencephalographic (SEEG) studies have found that the seizure onset zone (SOZ) in such patients may be in the nodule, overlying cortex, the connected medial temporal region, or a combination of the above. Here we present the use of three less commonly used techniques in North America, resulting in seizure freedom in a patient with PVNH. A 27-year-old right-handed woman, with a normal neurologic exam and medically refractory focal epilepsy since age six years presented with two distinct seizure semiologies - the first seizure type consisted of a behavioral arrest, loss of contact, and both oral and manual automatisms; the second seizure with complex motor behaviors. Scalp EEG revealed left temporal slowing and epileptiform discharges with colocalized seizure onset. MRI was remarkable for two PVNH in the posterior temporal trigone of the left lateral ventricle. Given these findings, SEEG implantation included medial and basal temporal structures, the PVNH and overlying cortex. Numerous electroclinical seizures were captured. The first and most common seizure type arose from left mid temporal gyrus-anterior occipital gyrus and left temporal gyrus. The second with complex motor behaviors arose from a network including the right temporal pole. To help understand the left temporal and PVNH network we next performed 1 Hz electrical stimulation from early ictal contacts and the PVNH. Stimulation of the anterior heterotopia (aHet) elicited CCEPs from the early ictal network associated with type 1 semiology. We next performed wavelet analysis of seizure onset and found ~100 Hz activity in early ictal contacts, but also including the PVNH, where high amplitude rhythmic activity was not clear as the seizure progressed. We hypothesized that the unorganized nature of PVNH tissue may reduce the higher amplitude synchronous field potentials that are recorded from normal tissue. We thus performed RF-TC of the PVNH alone as a possible step-wise approach to treatment. The patient has been seizure-free for more than two years in the context of continued monotherapy. This case report highlights the utility of CCEPs, signal processing, and RF-TC in epilepsy, particularly in the context of PVNH. We continue to examine the role of signal processing, connectivity analyses, and minimally invasive techniques in the treatment of epilepsy.

353. Status Epilepticus as an Extreme Presentation of Dialysis Disequilibrium Syndrome

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Introduction: Dialysis disequilibrium syndrome (DDS) is a rare syndrome characterized by neurological symptoms of

varying severity ranging from headaches, restlessness, blurred vision to seizures, coma or even death.

Case Summary: Our patient is a 46-year-old male with ESRD who is non-adherent with outpatient dialysis. He presented to the emergency department with altered mental status after he missed dialysis for 2 weeks. He was confused but awake and following commands. BUN was 85 mg/dl, K was 6.1 mmol/L, and CT Head didn't show any acute intracranial abnormality. He required emergent dialysis to treat underlying hyperkalemia and suspected uremic encephalopathy. Mannitol was given as a preventive measure to decrease the risk of DDS. Three hours into dialysis the patient had two observed generalized-onset seizures theb became obtunded and was intubated to protect his airway. BUN after dialysis was 28 mg/dl and repeat CT Head showed interval development of diffuse brain edema. Mental status improved steadily to neurologic baseline after 3 days of supportive treatment.

Discussion: DDS is a rare neurological syndrome with a wide range of presentations from mild headache and blurred vision to seizures or coma. Cerebral edema due to the rapid reduction in BUN which lowers plasma osmolarity and subsequently leads to water shift into the brain cells is the main pathogenesis[1]. Risk factors are first dialysis treatments, markedly high BUN > 175mg/dl, severe metabolic acidosis, age extremes and pre-existing neurologic diseases[2]. Our patient has been on dialysis for 3 years but was getting dialysis sessions once every 2-4 weeks. These long intervals between dialysis sessions could have possibly increased his risk to develop DDS. Measures to prevent DDS should be implemented in high-risk patients which include shorter periods of dialysis (around 2 hours) with a low blood flow rate (150-250 ml/min), and repeated dialysis daily with cautious increments in dialysis time and blood flow rates with close monitoring until the patient can be continued on established thrice weekly schedule. The utility of IV Mannitol has not been established and further research is needed. Treatment is mainly supportive. Dialysis should be stopped immediately, hypertonic saline and IV Mannitol have also been used to treat DDS but their efficacy and safety are not well established.

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354. Near-Fainting with Swallowing: Two Cases of Swallow Syncope

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Introduction: Swallow syncope is defined as loss of consciousness during or after swallowing, and is a rare cause of syncope. It is primarily a type of neurally mediated reflex syncopal syndrome which usually results in bradyarrhythmias and hypotension. Here we report two cases with syncopal episodes during different phases of swallowing.

Case Report: 58-year-old man with coronary artery disease and hypercholesterolemia was referred to neurology clinic for episodic lightheadedness upon taking first sip of water or first bite of food for decades. His symptoms occurred exclusively during meal times and lasted less than a minute. Vital signs were negative for orthostatic hypotension. Transthoracic echocardiogram showed preserved left ventricular systolic and diastolic function, and no valvular abnormalities. MRI/MRA brain were unremarkable. 30-day Holter event monitor captured multiple episodes of sinus tachycardia with average rate of 160/min approximately, which correlated with his symptoms of episodic lightheadedness, again occurring exclusively during meal times.

Our second case is of a 73-year-old man with diabetes mellitus type II with peripheral neuropathy seen in neurology clinic for episodes of near syncope for one year during the later half of his meal. These episodes would last seconds and were not related to the type of food intake. Vital signs were negative for orthostasis. CTA head and neck did not reveal any flow limiting stenosis.

Conclusion: Our two cases with swallow syncope emphasize the role of abnormal reactivity to esophageal and/or gastric mechanoreceptors at different levels in the pathophysiology of this rare condition. It is possible that anatomical location and extent of mechanoreceptor stimulation may result in slightly different clinical presentations of these cases. Additionally, swallow syncope is most commonly known to be associated with bradyarrhythmias. In contrast, our first patient's symptoms were strongly associated with sinus tachycardia.

355. Voltage-Based Algorithmic Detection of Postictal Generalized Electroencephalographic Suppression

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Introduction: Postictal generalized electroencephalographic suppression (PGES) is the dampening of electroencephalographic (EEG) activity below 10 microvolts following termination of generalized seizures. In patients with epilepsy, PGES lasting longer than 50 seconds has been associated with increased risk of sudden unexplained death. In the context of electroconvulsive therapy (ECT) for psychiatric illnesses, the presence of PGES has been associated with improved therapeutic outcomes. Despite existing voltage-based criteria for assessing PGES by visual inspection, expert clinical reviewers show poor concordance when determining the duration of this bioelectric marker. An automated, validated algorithm may be useful for reliably quantifying duration of PGES.

Methods: We investigated PGES following ECT administered for treatment-resistant depression. EEG data were obtained from recordings of 11 patients undergoing a total of 50 ECT-induced seizures. We developed a voltage-based detection algorithm that applies existing EEG amplitude criteria for PGES. This algorithm utilized a routine clinical longitudinal bipolar montage to simulate expert epileptologist readings. One-second windows were binarized into PGES or non-PGES based upon the number of channels with peak rectified amplitude below 10 microvolts. We validated the algorithm's performance by assessing its concordance with four expert clinical epileptologists' readings.

Results: Epileptologist ratings showed low-to-moderate concordance when rating PGES in the postictal period. Algorithmic detection displayed high discriminability when using individual epileptologists' ratings as gold standard measures, with c-statistics ranging between 0.88-0.92. After optimization of channel thresholding, the algorithm was compared to consensus clinical ratings of PGES and displayed high discrimination and agreement statistics, with a c-statistic of 0.92 and Cohen's Kappa of 0.63. Cohen's Kappa statistics measuring interrater reliability of the algorithm in relation to individual epileptologists was equivalent or superior to measures of reliability between individual epileptologists.

Conclusion: Amplitude-based algorithmic detection of PGES displays satisfactory reliability and discrimination statistics in comparison to expert clinical epileptologists' ratings. Improved detection of PGES may improve prediction of outcomes in patients with generalized seizures. Future directions include validation of algorithmic performance on independent datasets, including on recordings from patients with epileptic seizures.

356. Non-Convulsive Seizure as Initial Manifestation of Posterior Reversible Encephalopathy Syndrome (PRES)

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Introduction: PRES is typically subacute at onset and characterized by impaired consciousness, headache, vision abnormalities, seizures, nausea, vomiting, and focal neurological signs. Impairment of consciousness may range in severity from confusion, somnolence, and lethargy to encephalopathy or coma. Nonconvulsive seizure is characterized by electrographic seizure activity on EEG associated with minimal or no motor movements, typically with associated alteration of awareness. It is very important to know that PRES patients with impaired consciousness may have nonconvulsive seizure activity, which may be mistaken commonly for postictal confusion or altered mental status due to other causes.

Case Report: A 34-year-old female with history of morbid obesity, HTN, DM II, CKD presents with AMS in the setting of uncontrolled HTN, hyperglycemia & AKI on CKD. As per mother, patient had been reporting headaches, nausea, and vomiting for the last week. In ED, blood pressure was 261/142, and labs showed Na 129mmol/L, K 5.1mmol/L, glucose 516mg/dl, CO2 21mmol/L, Cr 2.39 mg/dl, Hgb A1c 12.1%, lactic acid 1.26mmol/L, prerenal AKI, and metabolic acidosis. UDS negative. CXR and UA normal. COVID test negative. CT head with no acute intracranial pathology. Exam significant for A&Ox0, not following commands, no blink to threat bilaterally, pupillary reflexes sluggish, and intermittent withdrawal to pain on all extremities. MRI showed DWI signal abnormality in the bilateral parieto-occipital regions. MRA unremarkable. Infectious workup negative. Mentation did not improve with BP control and glycemic control. EEG showed focal nonconvulsive seizure activity in the right temporo-occipital region. Phenytoin was then started, and subsequently the electrographic seizure activity stopped, coinciding with significant improvement in mentation. By the next day she was A&Ox2 with no agitation.

Conclusion: Chronic kidney disease and acute kidney injury are both commonly present in patients with PRES. In a patient with renal disease, hypertension, and rapidly progressive neurologic symptoms, it is essential to consider PRES in the differential diagnosis. Patients may present with nonconvulsive seizure activity contributing to alteration of awareness. It was reported that nonconvulsive seizure occurred in 3 out of 46 patients with PRES. Nonconvulsive status should be suspected in patients with prolonged states of altered consciousness. Our patient's mentation improved after treatment of her nonconvulsive seizure activity. Therefore, in addition to optimal BP management, timely diagnosis and treatment of nonconvulsive seizure activity are essential for patient recovery.

357. A Case Report of Mesial Temporal Lobe Epilepsy Misdiagnosed as Cyclic Vomiting Syndrome

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Background: Patients with seizures arising from the mesial temporal lobe often present with impairment of consciousness or awareness. Well-known characteristics of mesial temporal lobe seizures include auras, ictal automatisms, and changes in heart rate. However, rarer manifestations of mesial temporal lobe seizures can be easily misdiagnosed or confused with other medical etiologies. We present the case of a young woman with right hemispheric seizures presenting with repetitive vomiting and an initial diagnosis of cyclic vomiting syndrome.

Case: A 31-year-old Caucasian female previously diagnosed with cyclic vomiting syndrome with no official diagnosis of epilepsy presented to the hospital with her third lifetime generalized seizure. This was accompanied by several days of what the patient described as intractable nausea and vomiting. She reported that for most of adulthood, she had recurrent episodes of nausea and vomiting every few months, each of which would last for approximately one to two weeks. During these periods, she self-medicated with marijuana to help alleviate her symptoms. On initial evaluation, she was found to have a low serum phosphate level, and her seizure was thought to be provoked secondary to electrolyte derangements. She was monitored on continuous EEG, and her

electrolytes were corrected to within normal limits. However, even after electrolyte repletion, a total of 15 seizures arising over the right cerebral hemisphere were captured electrographically in 48 hours, all of which were maximal in the temporal region. Some of these events clinically correlated to lip smacking and severe nausea. She underwent brain MRI with and without contrast, which showed increased T2 flair signal arising from the right hippocampus. She was initiated on levetiracetam and lacosamide. To date, she has not had recurrence of her seizures.

Discussion: Seizures arising from the temporal lobe can present with highly variable symptoms and may be misdiagnosed, which can lead to lack of appropriate treatment for a number of years. Current literature notes that ictal emesis is associated with temporal seizures and typically non-dominant lateralization. The aforementioned patient was diagnosed with cyclic vomiting syndrome due to stereotypical episodes of vomiting and marijuana use. It is imperative to include epileptic seizures on the list of possible diagnoses in patients with otherwise unexplained nausea and vomiting to allow for earlier diagnosis and treatment.

358. Risk Factors Associated with Hyperammonemia Following Unprovoked Convulsive Seizures - Systematic Literature Review

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Background: Hyperammonemia has been reported in association with generalized convulsive seizures. As a result, serum ammonia levels have been frequently used in the emergency department to distinguish convulsive seizures from non-convulsive and non-epileptic seizures, as it is a cheap, and readily available test. In several studies, ammonia levels have been measured for patients presenting with seizures. Here, we have completed the first systematic literature review in an effort to find an association between hyperammonemia at presentation for an unprovoked convulsive seizure and potential associations, with the hope of elucidating the true diagnostic value of a serum ammonia level.

Design/Methods: A systemic review of the PubMed database was completed using the PRISMA guidelines. Keywords used to define the search included: "Seizure" and "Hyperammonemia". 302 Studies were found. Case reports, studies that had patients on Valproic Acid, literature reviews, pediatric, non-English, and animal studies were excluded. Studies that focused on patients with underlying metabolic disorders or malignancies that predisposed them to seizures were also excluded.

Results: Four studies met the inclusion criteria. The hyperammonemia cohort had a greater proportion of males than females (77.4% v. 22.5%, respectively, $p < 0.0001$). However, there was no difference in the proportion of males or females in the non-hyperammonemia cohort (51.8% v. 48.1%, respectively, $p = 0.38978$). Two studies were used to study the difference in average ammonia levels in patients with unprovoked seizures. As expected, the hyperammonemia patients with convulsive seizures had a significantly greater ammonia level ($p = 0.02561$) than the non-hyperammonemia cohort. Due to limitations in the number of studies, an analysis could not be conducted on differences in ammonia levels between convulsive v. non-convulsive seizures.

Discussion: Review of the literature suggests that male patients presenting with unprovoked convulsive seizures have higher ammonia levels. While this review confirms the diagnostic role potential ammonia levels have, it is limited by the lack of studies that have followed these patient cohorts over time. Further analysis is warranted to analyze the role of ammonia in acute presentation of patients with epilepsy.

359. Clinical, Radiographic, and Electroencephalographic Findings of Seizures Associated with Stroke: A Retrospective Study

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Background: Cerebrovascular disease is a common cause of seizures, especially in older adults. Data from the stroke registry has shown 5-20% patients with stroke develop seizures.

Objective: To evaluate the clinical, radiographic, and electroencephalographic findings and outcomes of patients with seizures associated with stroke.

Methods: This is a retrospective study of database from comprehensive stroke and epilepsy center for patients evaluated between 2017-19. Early-onset seizures was defined as seizure occurrence in the first 7 days after stroke, and late-onset after 7 or more days. Data was stratified based on age, type of stroke (ischemic vs hemorrhagic), location (cortical vs subcortical), and the vascular territory involved based on careful review of available imaging studies.

Results: Of the 1665 patients with seizures in our epilepsy database, 135 (8.10%) patients had post-stroke seizures. The mean age was 64.17 ± 15.86 years, and the median age of seizure onset was 55.45 ± 18.68 years with 51.12% men and 49.83% women. 8.14% patients had early-onset and 91.85% patients had late-onset seizures. Ischemic stroke was found in 73.33% of patients, hemorrhagic stroke in 22.96%, and ischemic stroke with hemorrhagic transformation per ECASSIII classification in 2.22% of patients. 66.6% patients had only cortical involvement, 18.51% had both cortical and sub-cortical involvement, whereas 12.59% were unknown. Location of the stroke was middle cerebral artery (MCA) in 73.33% patients, followed by anterior cerebral artery (ACA) in 17.77% patients and posterior cerebral artery (PCA) in 11.11% patients. Focal seizures are found in 62.96%, and focal to bilateral tonic-clonic in 36.29%. Lobar involvement based on EEG findings were temporal in 50.37%, frontal in 22.22%, parietal in 5.91% and occipital in 2.22%. EEG findings in these patients were generalized slowing in 27.40% and focal slowing in 5.18%. Focal epileptiform activity was seen in 34.81%. EEG was normal in 32.59%. Approximately 83% of patients were not well controlled and 26.6% met the criteria for intractable epilepsy. Only 17.03% achieved seizure freedom. Status epilepticus occurred in about 4.24% of patients.

Conclusion: Cerebrovascular disease is a common cause of seizures comprising approximately 8% of patients in our

database. Most patients had late onset of seizures (mean duration 10.1 years). Focal seizures were the most common type and temporal lobe involvement was most often noted in patients with seizures. The outcome of post-stroke seizures was poor as only 17% of patients achieved a seizure free state.

K-587. **Prehospital Midazolam Use And Outcomes Among Patients With Out-of-hospital Status Epilepticus**

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Objective: To examine the use of evidence-based benzodiazepine administration and the association between low benzodiazepine dose, breakthrough seizures, and respiratory support in patients with status epilepticus.

Methods: This is a cross-sectional analysis of adult patients with status epilepticus treated by an emergency medical services (EMS) agency from January 2013 to January 2018. The primary outcome was the need for rescue therapy, an indicator for breakthrough seizure and defined as treatment with a second benzodiazepine dose. The secondary outcome was the need for respiratory support. Midazolam was the only benzodiazepine administered.

Results: Among the 2,494 cases of status epilepticus, mean age was 54.0 years and 1,146 (46%) were female. There were 1,537 patients given midazolam at any dose, yielding a benzodiazepine administration rate of 62%. No patients received a dose and route consistent with national guidelines and of the 943 patients who received a dose of midazolam that was 5mg or higher, 938 (99.5%) received a dose of 5mg and only 5 patients (0.5%) received a dose greater than 5mg. Rescue therapy with a second dose of midazolam was required in 282 (18%) patients. Higher doses of midazolam were associated with lower odds of rescue therapy (OR 0.8, 95% CI 0.7-0.9) and the probability of requiring rescue therapy was considerably lower among those who received 10mg as compared to 1mg of midazolam (4.5% versus 32.3%, respectively using average marginal effects). Higher doses of midazolam were not associated with increased need for respiratory support. If anything, in the adjusted analysis, higher doses of midazolam were associated with decreased need for respiratory support (OR 0.9, 95% CI 0.8-1.0).

Conclusions: An overwhelming majority of patients with status epilepticus did not receive evidence-based benzodiazepine treatment in the prehospital setting. Higher midazolam doses were associated with reduced use of rescue therapy and there was no evidence of respiratory harm suggesting that benzodiazepines are being withheld without clinical benefit.

K-589. **Epileptic Encephalopathy in Kcna1 KO Mice Disrupts Active State Organization**

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Rationale: In patients with epileptic encephalopathy (EE), severe cognitive and behavioral dysfunction is thought to be principally mediated by pervasive and often intractable seizures. Several genetic etiologies of EE have been identified, including homozygous mutations in KCNA1, which encodes a ubiquitously expressed voltage gated potassium channel subunit. Prior attempts at demonstrating features of "encephalopathy" in such EE models have employed task-based assays of spatial learning or exploration, which are brief unidimensional assessments that are often confounded by human exposure and unconscious bias. In this study, we applied instrumented home-cage monitoring and wireless EEG to noninvasively visualize perturbations in higher-order patterns of spontaneous murine behavior that may represent more ethologically sound correlates of encephalopathy.

Methods: 6-8 week old WT (27) and KCNA1 KO (22) littermates were assessed in instrumented home-cage chambers (Noldus Phenotypers) for 48-72h, designed to simultaneously tally movement, sheltering, feeding, licking and behaviorally defined sleep. A separate group of KO mice (n=5) were similarly assessed in these chambers with simultaneous wireless EEG recordings (EMKA Technologies).

Results: As described by Tecott (2008 PNAS), WT mice oscillated between two discrete behaviorally defined states: active (patrolling, foraging) and inactive (sleep, quiet wakefulness). KO mice displayed significantly more active states that were morphologically longer in duration and which accumulated greater distances. When examined with simultaneous EEG recordings, spontaneous seizures predominantly emerged from active states. Valproic acid treatment improved seizure frequency and active state durations without affecting the mean number of daily active states.

Conclusions: Our results reveal that an ion channel, designed to regulate neuronal excitability at millisecond timescales, pleiotropically modulates fundamental higher-order temporal features of behavioral organization. We hypothesize that disrupted active state structure in Kcna1 KO mice is a correlate of an encephalopathic state, with distinct epileptic (anticonvulsant-remediable) and underlying static/lesional (non-remediable) components. Ongoing experiments seek to employ a genetic approach to understanding the developmental contributions of Kcna1 loss, and how KCNA1-associated proteins (including LGI1, CNTNAP2, STARGAZIN) modulate active state morphology.

K-599. **Models And Mechanisms Of DEPDC5-related Epilepsies**

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Focal cortical dysplasia (FCD) is the most common underlying pathology in children with drug-resistant epilepsies. Low-frequency somatic mutations in key genes within the mechanistic target of rapamycin (mTOR) pathway have been discovered in patients with FCD, hemi-megalencephaly

or megalencephaly, suggesting that these phenotypes constitute a single broad spectrum of developmental brain disorders with shared molecular etiologies and neuropathological features. GAP activity toward RAGs complex 1 (GATOR1)-encoding genes germline mutations have been recognized as the most important genetic cause in familial focal epilepsies with FCD, offering exciting opportunities to mechanistically understand their epileptogenesis and ictogenesis. However, it remains elusive how GATOR1 sculpts neurodevelopment and how its mutations generate cortical dysplasia and epilepsies. Here, we first show a novel focal Depdc5-related epilepsies model with anatamo-electro-clinical signatures that are highly clinically relevant to human FCD II, including distinct focal interictal and ictal fingerprints of human FCD. Then, we show how DEPDC5 mutations lead to both cell-autonomous and non cell-automous dysregulation of excitatory and GABAergic networks and establish the underlying molecular logics and networks to mechanistically understand the hyperexcitable cortex and seizures. Lastly, we show how a novel therapeutic drug improve the seizure control.

K-601. Repetitive Transcranial Magnetic Stimulation to Assess Cortical Plasticity & Suppress Spikes in Pediatric Epilepsy

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Introduction: Children with benign epilepsy with centrotemporal spikes (BECTS), the most common pediatric epilepsy syndrome, have a mild seizure disorder but have moderate language difficulties, the pathophysiology of which is currently unknown. Many posit that interictal epileptiform discharges (IEDs) arising from one or both motor cortices disrupt language development, possibly by driving atypical interactions between the motor and language networks. Transcranial magnetic stimulation paired with EMG and EEG (TMS-EMG, TMS-EEG) is a unique tool for studying brain dynamics that directly assesses the downstream impact of the stimulated cortex. Furthermore, repetitive trains of TMS (rTMS) induce focal changes in cortical excitability and thus is a potential therapy for IEDs. We piloted the use of TMS-EMG-EEG in children with BECTS to assess if electrophysiologic properties of the motor cortex correlate with language function and to determine if rTMS reduces IEDs.

Methods: Nine right-handed children with BECTS underwent assessments of IQ, attention, and language learning (California Verbal Learning Task-Children's Edition). Children then underwent TMS-EMG-EEG of the left motor cortex. We measured the baseline amplitude of TMS-EEG evoked potentials (TEPs) and then applied 1 Hz repetitive TMS (rTMS) to induce long term depression (LTD)-like changes. We compared post-rTMS TEP amplitudes to pre-rTMS amplitudes to quantify use-dependent plasticity and assessed if plasticity correlated with learning scores. Finally, we counted IEDs 10 minutes before and after rTMS to measure the effect of rTMS on IED frequency.

Results: Children with BECTS tolerated TMS; no seizures were provoked. rTMS-induced changes in TEP amplitude strongly correlated with scores on the language learning task ($r = 0.71$, $p = 0.03$) even after adjusting for full-scale IQ or attention. Six children had IEDs during the baseline period; the 3 others did not have IEDs before or after rTMS. Five of six children had a reduction in IED frequency after rTMS (reduction of 1-92 IEDs/10minutes) and one child had an increase (increase of 49 IEDs/10minutes); the child with the increase had exclusively right-sided discharges while the other children had left or bilateral IEDs.

Conclusions: TMS is safe and feasible for children with BECTS. Motor cortex plasticity predicts not only motor but also language learning, suggesting a mechanism by which motor cortex seizures may interact with language development. Future studies will use TMS-EEG based connectivity measurements to assess the impact of IEDs on connectivity and to more definitively assess if rTMS reduces IEDs in BECTS.

Global Neurology

141. Machine Learning the Neurological Manifestations of Covid-19 from Literature

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Introduction: When a new virus is discovered and causes a pandemic, it is important to extract actionable information coming from all scientific sources to help combat the pandemic. A natural language processing (NLP) based bidirectional encoder representation from transformers (BERT) is proposed to automatically learn the neurological manifestations of the coronavirus disease 2019 (COVID-19) pandemic from the open research dataset (CORD-19). This machine learning tool indicates central and skeletal neurological and skeletal muscle injury manifestations.

Methods: COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through the angiotensin-converting enzyme (ACE2), resulting in an unprecedented pandemic with millions of infections and mortalities worldwide. Typical clinical manifestations include fever, cough, diarrhea and fatigue. In response to the pandemic, the White House led the creation of CORD-19 as a resource spanning thousands of scholarly articles on SARS-CoV-2. A semi-supervised literature understanding system that accepts natural language questions and returns specific answers from the CORD-19 scientific paper corpus is developed and is able to generate new insights into the neurological manifestations of COVID-19. The approach involves exporting the CORD-19 documents to database, stemming the natural language questions before passing as query, parsing the results, scoring and preparing summarized answer based on BERT. The machine learning model has vector of text elements with pre-defined vocabulary and features are count of each of these keywords. A classifier is then trained using the feature set and is used to predict attribute labels. Linguistic rules are used to label each sentence to help identify concise, data-driven statements.

Results: The semi-supervised literature understanding system found that patients with sever infection were more likely

to develop neurological manifestations, especially acute cerebrovascular disease, impaired consciousness and skeletal muscle injury. Some patients, especially older, may have severe infections and more underlying disorders but exhibit fewer typical symptoms and only show neurological manifestations. Central nervous system (CNS) are the main form of neurologic injury in COVID-19 patients along with lower lymphocyte counts.

Conclusion: The semi-supervised literature understanding approach is critical as the rapid acceleration in new coronavirus articles makes it difficult for the medical research community to keep up. The system suggests the clinicians to consider SARS-CoV-2 infection as a differential diagnosis when seeing COVID-19 patients with neurological manifestations. [1] Mao, Ling, et al. "Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China." JAMA neurology 2020.

142. Immune Reconstitution Inflammatory Syndrome (IRIS) in the Central Nervous System: Limitations for Diagnosis in Resource Limited Settings

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Background: The diagnosis of IRIS is based on evidence of clinical worsening and immune reconstitution in the setting of antiretroviral therapy (ART) initiation. While central nervous system (CNS) IRIS is thought to be prevalent in resource limited settings (RLS), its identification is limited by an absence of data on pre-treatment HIV disease and diagnostic testing. The definitive diagnosis of CNS IRIS may require neuroimaging and cerebrospinal fluid (CSF) studies, which are not universally available in RLS. To determine the feasibility of making a diagnosis of CNS IRIS can be made in a RLS in Africa, we completed a retrospective analysis of research records at a tertiary care facility in Lusaka, Zambia.

Methods: We performed a retrospective review of HIV+ individuals in two cohort studies of suspected CNS opportunistic infection at a tertiary care hospital in Zambia. Eligible participants were HIV+ and on ART at the time of neurologic presentation. We recorded information regarding HIV history, clinical presentation and neurological evaluation. We determined whether these patients met criteria for CNS IRIS based on the French Criteria published in 2004. If a diagnosis of CNS IRIS could not be made, data was assessed for an alternative diagnosis such as primary infection. Records were reviewed for diagnostic barriers.

Results: Of 902 study records, 254 met basic inclusion criteria. None of the participants could be diagnosed with CNS IRIS per the French Criteria as there was no information on post-treatment trajectory of HIV viral loads or CD4 counts. Only 7 (3%) patients received a complete diagnostic workup with comprehensive infectious testing in the CSF and neuroimaging. Forty-five (18%) received a comprehensive workup but no neuroimaging. The remaining 202 patients (79%) only received a partial infectious workup +/- neuroimaging. Only one participant had a definitive, non-IRIS diagnosis of PML based on comprehensive testing. Of the 254 patients, 68 (27%) had an identified potential CNS pathogen, 92 (36%) had inflammatory CSF in the absence of a pathogen, and 94 (37%) were without CSF abnormalities despite presenting with CNS symptoms.

Conclusion: The absence of baseline HIV data, and lack of comprehensive diagnostic testing, compounded by a high prevalence of infectious pathogens, limits the ability to diagnose CNS IRIS in resource limited settings even when additional resources for evaluations are available through research activities.

143. Evaluating the Impact of Antiretroviral and Antiseizure Medication Interactions on ARV Effectiveness among Outpatient Clinic Attendees in Zambia

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Objective: The decision to commence antiseizure drugs (ASDs) in a person with HIV is critical because interactions between enzyme-inducing anti-seizure drugs (EI-ASDs) and antiretroviral drugs (ARVs) can lead to ARV resistance. We conducted a study to determine if co-usage of ARVs and EI-ASDs is associated with ARV-resistant HIV among patients in Zambia.

Methods: Participants were identified and prospectively enrolled at 3 clinics in Zambia. Eligible participants were over 18 years of age, taking ASDs and ARVs for at least 1 month over the prior 6-month period. Participants answered questions regarding medication and HIV history. CD4 counts and plasma viral loads (pVL) were obtained, with HIV genotype obtained for pVL> 1000 copies/ml. Pearson's test of independence was used to determine significance of ASD regimen with pVL>1000 copies.

Results: We enrolled 50 participants- 82% were taking carbamazepine (37 as monotherapy, and 4 as combined regimen with another ASD), 14% were on phenobarbitone. No one had switched ASD regimens in the prior 6 months. Participants were on 13 ARV regimens, with 68% on a TDF/3TC backbone, and 94% on their present ARV regimen for the prior 6 months. Participants had a median CD4 nadir of 205 cells/mm3, and 60% had a highest documented WHO HIV stage of I or II. The mean CD4 count at study enrollment was 464 cells/mm3 (SD 226.3). Seven participants (14%) had a CD4 count <200 cells/mm3. Only

4 participants (8%) had a pVL >1000 copies, all of whom were on carbamazepine. Three of the 4 participants with elevated pVL had a CD4 count < 200 cells/mm3. None had documented adherence concerns; however, 2 had events concerning for clinical failure (TB and worsening seizures). HIV genotype testing showed mutations against nucleoside reverse transcritpase inhibitors and non-nucleoside reverse transcriptase inhibitors in 3/4 participants . Use of carbamazepine was not found to correlate with elevated pVL (p=0.58).

Conclusions: EI-ASDs are commonly used in sub-Saharan Africa. Despite concurrent use of EI-ASDs and ARVs, the majority of participants showed CD4 counts > 200 cells/mm3 and were virally suppressed. In this small study, carbamazepine did not appear to show any increased risk of developing virological failure or ARV-resistant HIV.

144. Prognostic Utility of Daily Changes in Glasgow Coma Scale and the Full Outline of Unresponsiveness Score Measurement in Patients with Metabolic Encephalopathy, Central Nervous System Infections and Stroke in Uganda

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Background: Metabolic encephalopathy (ME), central nervous system (CNS) infections, and stroke are common causes of reduced level of consciousness (LOC) in Uganda. However, the prognostic utility of changes in the daily measurements of the Full Outline of Unresponsiveness (FOUR) score and Glasgow Coma Scale (GCS) score in these specific disorders is not known.

Methods: We conducted secondary analyses of data from patients who presented with reduced LOC due to CNS infections, stroke, or ME to a tertiary hospital in Uganda. Patients had FOUR/GCS scores at admission, and at 24 and 48 hours. We calculated a change in FOUR score (ΔFOUR) and change in GCS score (ΔGCS) at 24 and 48 hours and used logistic regression models to determine whether these changes were predictive of thirty-day mortality.

Results: We analyzed data from 230 patients (86 with ME, 79 with CNS infections and 65 with stroke), mean (SD) age of 50.8 (21.3) years, 27% (61/230) had HIV infection and 62% (134/230) were peasant farmers. ΔFOUR score at 24 hours was predictive of mortality amongst those with ME (OR 0.64, 95% CI 0.48-0.84, p = 0.001), and those with CNS infections (OR 0.65, 95% CI 0.48-0.87, p = 0.004), but not in those with stroke (OR 1.0, 95% CI 0.73-1.38, p = 0.998). However, ΔGCS score at 24 hours was only predictive of mortality in the ME group (OR 0.69, 95% CI 0.56-0.86, p = 0.001), but not in the CNS or stroke groups. This 24-hour ΔGCS and ΔFOUR score pattern was similar at 48 hours in all subgroups.

Conclusion: Changes in daily FOUR and GCS scores are prognostic in Ugandan patients with CNS infections and ME, but not in those with stroke. Patients with reduced LOC due to stroke are more optimally monitored using stroke specific scales.

145. Where There is No Neurologist: Developing a Curriculum for a New Neurology Training Program in Zambia

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Objective: Describe a novel post-graduate neurology training program implemented in Zambia and a framework for implementing training in regions with no local neurologists.

Background: Zambia has a population of ~17 million people and a high neurological disease burden, but the entirety of neurologic care is currently provided by 4 expatriate neurologists. The first post-graduate neurology training program in the country was launched one year ago and is currently training the first generation of Zambian neurologists.

Methods: We describe the overall framework and novel aspects of the post-graduate curriculum for the first neurology training program in Zambia.

Results: Given the absence of local neurologists, heavy external support was needed from US and European neurologists, including one based in Zambia and dedicated full-time to the program. The program consists of 3 years of internal medicine followed by 2 years of neurology training, similar to other subspecialty programs in Zambia. The curriculum was designed to blend aspects of traditional Zambian and US post-graduate training. The curriculum is competency-based and assessed using individualized learning plans and personal portfolios. Post-graduate training in Zambia is considered a Master's degree with assessments usually weighted heavily on written and oral examinations. However, we incorporated monthly observed clinical examinations, documentation review, patient presentations and clinical assessments to diversify the assessments. Finally, we developed a weekly schedule consisting of journal clubs, case conferences, didactic lectures and a research methods seminar. In the first year, the three neurology trainees cared for ~1600 inpatients and completed >1000 outpatient visits. High patient volume with limited trainees, reliance on volunteers for clinical teaching and support, and tension between teaching to the setting and teaching what is possible were identified challenges.

Conclusions: We report successful implementation of a novel neurology post-graduate training program in Zambia which included features of traditional Zambian training with newer educational innovations from the US system.

146. The Influence of Sex on the Management and Outcomes of Individuals with Acute Traumatic Spinal Cord Injury: A Series of Propensity-Score Matched Cohort Studies

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Background: While few previous pre-clinical studies documented potential neuroprotective effects of estrogen/

progesterone, there is no conclusive clinical evidence on sex-related differences in outcomes after spinal cord injury (SCI). This study examined the potential effects of sex on injury epidemiology, management and outcomes after traumatic C1-L2 SCI.

Methods: A series of propensity-score matched cohort studies was performed comparing females in premenopause (age≤40 years), perimenopause (41>age≥50) and postmenopause (age>50), with males distributed similar age subgroups. In each subgroup analyses, females were matched on a 1:1 ratio to males using the propensity score matching on age at SCI onset, Charlson Comorbidity Index, and level and severity of SCI. Data for the studies were selected from the Rick Hansen Spinal Cord Injury Registry from April/2004 to September/2019 (n=5579 eligible cases). Females were compared with males regarding injury epidemiology (mechanism of SCI, ethnicity, Glasgow coma score [GCS], Injury Severity Score [ISS]), management (direct transfer to a spine center, need for mechanical ventilation, use of skeletal traction, administration of Methylprednisone, surgical versus conservative treatment, time from injury to surgical decompression), and outcomes after SCI (length of stay [LOS] in the acute care and rehabilitation facilities, ASIA motor and sensory subscores, Functional Independence Measure subscores, discharge destination, and frequency of spasticity).

Results: Among individuals younger than 41 years, females (n=320) more often were white (p=0.0268) and had SCI due to falls or transportation-related accidents (p=0.0014) than males (n=320), but both subgroups were comparable regarding GCS and ISS. Both subgroups under 41 had comparable management but females had more often surgical treatment (p=0.0326). Furthermore, there were no significant differences between females and males under 41 regarding outcomes. Among individuals between 41 and 50 years, females (n=133) were comparable to males (n=133) regarding the other not-matched baseline data, management, and outcomes. Among individuals older than 50 years, females (n=531) had more fall-related SCIs (p=0.0033) and shorter rehabilitation LOS (p=0.0205) than males (n=531). However, there were no significant differences between females and males regarding the other not-matched baseline data, management, and outcomes.

Conclusions: The results this series of propensity-score matched cohort studies suggest that sex is not a key determinant for the vast majority of management measures, and clinical, neurological and functional outcomes following traumatic C1-L2 SCI, when data analyses were controlled for major potential confounders.

147. Clinical and Microbiological Characteristics of Bacterial Meningitis in Adults

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Background: We investigated clinical, laboratory, and microbiological profiles of patients with adult bacterial meningitis from a single tertiary center over a 10-year period.

Methods: We retrospectively reviewed medical records of adult patients with laboratory-confirmed bacterial meningitis from 2007 to 2016. Patients with recent neurosurgery, head trauma, or indwelling neurosurgical devices were classified as having healthcare-related meningitis. Causative microorganisms were identified by analyzing cerebrospinal fluid (CSF) and blood cultures, and antimicrobial susceptibility profiles were evaluated. We performed multiple logistic regression analysis to identify factors associated with unfavorable outcomes.

Results: We identified 161 cases (age, 55.9 ± 15.5 years; male, 50.9%), of which 43 had community-acquired and 118 had healthcare-related meningitis. Median CSF white blood cell count was 828.0/mm^3 (interquartile range, 256.3-2,870.0), with 76.3% neutrophils. CSF and blood culture positivity rates were 91.3% and 30.4%, respectively. In community-acquired meningitis patients, *Klebsiella pneumoniae* (25.6%) was the most common isolate, followed by *Streptococcus pneumoniae* (18.6%) and *Listeria monocytogenes* (11.6%). Among healthcare-related meningitis patients, the most common bacterial isolates were coagulase-negative staphylococci (28.0%), followed by *Staphylococcus aureus* (16.1%) and *Enterobacter* spp. (13.6%). Neurological complications occurred in 39.1% of the patients and the 3-month mortality rate was 14.8%. After adjusting for covariates, unfavorable outcome was significantly associated with old age (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.00-1.06), neurological complications (OR 4.53, 95% CI 1.57-13.05), and initial Glasgow coma scale ≤ 8 (OR 9.33, 95% CI 2.57-33.91).

Conclusions: Understanding bacterial pathogens and their antibiotic susceptibility may help optimize antimicrobial therapy in adult bacterial meningitis.

148. Age-Adjusted Outcomes of COVID-19 Among Patients with Pre-Existing Cerebrovascular Disorders

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Background: Coronavirus Disease 2019 (COVID-19) infection is an ongoing pandemic with high worldwide mortality. It affects mainly the respiratory system and the few who have severe symptoms end up requiring ventilators. Very few studies on epidemiological characteristics have been published, showing the prevalence of comorbidities including cerebrovascular diseases (CeVD) but outcomes of such patients with pre-existing CeVD are unknown.

Objectives: The aim of the study was to evaluate the prevalence of CeVD and age-adjusted outcomes (mortality and needs of mechanical ventilation) of COVID-19 patients among pre-existing CeVD.

Methods: We conducted systematic review, searching PubMed for original full-text observational studies that

described epidemiological characteristics of patients with COVID-19 using ((COVID-19[Title/Abstract]) OR coronavirus[Title/Abstract]) OR SARS-CoV-2[Title/Abstract] OR 2019-nCoV[Title/Abstract] and following MOOSE protocol. Literature other than observational studies, non-English literature, non-full text, and animal studies were excluded. Abstracts were reviewed, and articles were retrieved only if they mention CeVD or stroke as one of the pre-existing comorbidities. We used comprehensive meta-analysis software to get the pooled prevalence of CeVD and the outcomes (mortality and needs of mechanical ventilator) and heterogeneity (I^2) in the meta-analysis. Random effects model meta-analysis was conducted to calculate the unadjusted and age-adjusted correlations (r) and determination of correlation (R-squared) between CeVD and outcomes. We used age >50-years for the age-adjusted analysis (>50-years vs. <=50-years). p<0.05 was considered as significant.

Results: We found 7-studies mention details on CeVD out of 23-studies described epidemiological characteristics of COVID-19. 5 out of 7 studies have mentioned details on outcomes (mortality and needs for mechanical ventilator). Pooled prevalence of CeVD comorbidity was 5.03% [95%CI:3.3%-7.6%; I^2:51.7%; p<0.0001; 53/1087 patients]. Amongst those five studies, pooled prevalence of mortality was 17.2% [95% CI:7.6%-34.6%; I^2:93.76%; p<0.0001; 147/792 patients] and needs of mechanical ventilator was 24.5% [95% CI:11.5%-44.6%; I^2:93.94%; p<0.005; 158/608 patients]. On unadjusted regression analysis, mortality [r:0.62; R-squared:0.38; I^2:93.76%; p<0.0001] and needs for ventilators [r:0.56; R-squared:0.31; I^2:93.94%; p<0.0001] were significantly associated with pre-existing CeVD. On age-adjusted analysis, older patients >50-years had stronger association between mortality and CeVD [r:0.66; R-squared:0.43; I^2:93.76%; p<0.0001] and needs of mechanical ventilator and CeVD [r:0.71; R-squared:0.51; I^2:93.94%; p<0.0001] in compare to patients younger than 50-years.

Conclusion: COVID-19 patients with pre-existing CeVD have poor outcomes and more observational studies should be performed to validate these findings as well as to evaluate the role of COVID-19 in developing new CeVD and stroke due to its pro-inflammatory and hypercoagulation states.

149. Prevalence of Epilepsy in Latin America and the Caribbean (LAC): A Systematic Review and Meta-Analysis

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Introduction: Epilepsy is one of the most common and burdening neurological conditions. Worldwide, the estimate of prevalence varies significantly among countries. The prevalence estimate is an important epidemiological measurement to guide public health interventions. In Latin America and the Caribbean (LAC), the data suggest important heterogeneity. Nevertheless, there is not an updated synthesis that analyzes the overall prevalence of epilepsy in this region.

Aim: To estimate the overall prevalence of epilepsy in LAC.

Methods: We conducted a systematic review with meta-analysis. We performed a search up until March 2020, including observational studies that assessed the prevalence of epilepsy in LAC countries, despite the language of publication. We searched in PUBMED, LILACS, and SCOPUS databases. Later, the data was selected and extracted by groups of two independent researchers. For the pooled prevalence estimates, meta-analyses were performed with a random-effects model, adjusting by Freeman-Turkey double arcsine transformation. Additionally, we estimated values according to the setting (rural vs urban), health-related outcomes region classification (from the WHO-Choice study), ILAE's classification, and etiology. Sensitivity analysis was carried according to relevant studies' characteristics. The protocol was registered in PROSPERO (CRD42018091220).

Results: We included 32 population-based studies (n=317 104). The point prevalence of epilepsy was 14.99 per 1,000 inhabitants (95% CI: 12.29 - 17.94), while the active prevalence was 9.47 per 1,000 individuals (95% CI: 7.58 - 11.54). The overall prevalence of epilepsy was higher in rural areas, 17.48 per 1,000 persons (95% CI: 12.81 - 22.84); and in countries with poor health-related outcomes (Region D), 20.95 per 1,000 (95% CI: 16.77 - 25.57), predominantly in Guatemala and Ecuador. Epilepsies of genetic, immunological, and metabolic etiologies (4.30 per 1,000 persons [95% CI 0.05 - 14.58]) and those with focal seizures (4.36 per 1,000 persons [95% CI 2.79 - 6.26]) had the highest prevalence. The overall prevalence of epilepsy due to neurocysticercosis (NCC) was 2.90 per 1,000 persons (95% CI 0.05 - 6.69). The heterogeneity measure (I^2) ranged from 68.69 to 99.09%.

Conclusions: The epilepsy prevalence in LAC is higher than worldwide estimates. The prevalence is higher in rural areas and those with focal seizures. We identified high heterogeneity between studies and significant methodological gaps (e.g., incorrect sampling, lack of longitudinal studies), and clinical gaps (etiologies and role of NCC). Further standardization on designing and reporting of epidemiologic studies of epilepsy is needed.

150. Predictors of Stroke Mortality in Zambia

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Objective: Determine predictors of mortality amongst patients with stroke in Zambia.

Background: Stroke is the second leading cause of mortality worldwide. Stroke burden in sub-Saharan Africa (SSA) is one of the highest in the world. However, systematic studies of stroke mortality and outcomes in SSA are lacking.

Methods: We completed a prospective cohort study of consecutive stroke patients admitted to the University Teaching Hospital in Lusaka, Zambia between October 2018 - April 2019. Standardized data collection instruments were used to prospectively capture pertinent patient demographic, clinical, laboratory and imaging results, stroke subtype classification, and final in-hospital outcomes. Phone calls and clinic registers were used to determine ninety-day outcomes. Descriptive statistics are reported, and t-tests were used to compare continuous variables and chi-square analyses for categorical variables.

Results: 320 stroke patients were enrolled with an average age of 60 (SD 18) years and 62% (n=201) female. Stroke subtypes were 57% ischemic, 29% hemorrhagic, and 14% unknown (i.e. no CT scan performed during hospitalization). Risk factors for both in-hospital and ninety-day post-discharge mortality included lower GCS [in-hospital: 8.0+3 (dead) vs 11+3 (alive), p<0.001; 90-day: 9.8+3.4 vs 11.7 +3.3, p=0.02], fever during hospitalization (in-hospital: 27% vs 12%, p=0.001; 90-day: 22% vs 9%, p=0.01),abnormal mental status exam (in-hospital: 93% vs 49%, p<0.001; 90-day: 72% vs 41%, p0.001), aspiration pneumonia (in-hospital: 34% vs 10%; 90-day: 31% vs 5%; p's<0.001) and NG tube placement during hospital admission (in-hospital: 35% vs 16%; 90-day: 41% vs 9%, p's<0.001). Additional factors associated with in-hospital mortality included hemorrhagic stroke (p=0.01), higher ICH score (among hemorrhagic strokes), symptom progression after stroke onset (p=0.02), abnormal triglycerides (p=0.046), higher creatinine (p<0.001) and admission to the ICU (p=0.04). Finally, older age (p<0.001) and higher temperature 24-hours post-stroke were also associated with ninety-day post-discharge mortality.

Conclusion: Our results show higher mortality in patients with severe stroke symptoms and prior history of stroke. In-hospital complications such as aspiration pneumonia, NG tube requirement, and fever were associated with both in-hospital and post-discharge mortality. Our data highlights the necessity of optimizing in-hospital stroke management in order to minimize in-hospital complications such as fever and aspiration pneumonia as these affect not only in-hospital mortality but also 90-day post-discharge mortality.

151. Inpatient Stroke Epidemiology in Zambia

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Objective: Describe stroke epidemiology in Zambia including stroke subtype (ischemic vs. hemorrhagic), risk factors, and in-hospital mortality.

Background: While stroke burden has remained constant in high-income countries, it has significantly increased in low- and middle-income countries including those in sub-Saharan Africa (SSA). However, systematic studies of stroke epidemiology and outcomes in SSA are lacking.

Methods: Standardized data collection instruments were used to prospectively collect pertinent patient demographic, clinical, laboratory and imaging results as well as in-hospital mortality for consecutive stroke patients admitted to the University Teaching Hospital in Lusaka, Zambia between October 2018 - April 2019. Strokes were classified as ischemic stroke (IS) or hemorrhagic stroke (HS) based on CT appearance. Patients without neuroimaging were classified as unknown stroke (US). Descriptive statistics were calculated and compared between ischemic and hemorrhagic stroke using t-tests for continuous variables and chi-square analyses for categorical variables.

Results: 320 stroke patients were enrolled with an average age of 60 (SD 18) years and 62% (n=201) female. Stroke subtypes were 57% IS, 29% HS, 14% US. Compared to other subtypes, patients with IS were significantly more likely to be female (p=0.001), and those with HS were significantly younger (p=0.001). Stroke risk factors included: hypertension (80%), heart disease (34%), HIV infection (17%), hyperlipidemia (14%), diabetes (16%), and atrial fibrillation (9%). Diabetes (p=0.01), heart disease (p=0.008), and atrial fibrillation (p<0.001) were significantly more prevalent in IS. In-hospital mortality for all strokes was 24% and was significantly higher in HS (29%, p<0.01).

Conclusion: This Zambian stroke cohort is notable for their young age, extremely high rate of hypertension, and over-representation of HIV infection (national prevalence: 12%). Our results reflect the growing burden of stroke in Zambia, the significant role of HIV infection, and the need to improve hypertension diagnosis and treatment for primary stroke prevention.

152. A Super Smeller Who is Allergic to Chemical Smells-Multiple Chemical Sensitivity Induced Hyperosmia

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Introduction: The cause of Hyperosmia has not been well understood till date. GABA and Glutamate in the olfactory bulb are postulated to be essential in the olfactory response to a stimulus *(Gordon M. Shepherd, 2007)* and also in the pain pathway. Chemical induced disturbances in the release of GABA produced by Granule cells, can no longer inhibit the Mitral and Tufted cells producing Glutamate, which can lead to olfactory signals being sent to the brain even at a low smell threshold. This may be the cause of Hyperosmia in multiple chemical sensitivity(MCS) patients and this decrease in GABA is also responsible for the pain experienced by these patients. Such a case is presented.

Case Study: This 35 yr old woman presented with hyperosmia and burning tongue. She has MCS and hyperosmia since 3 yrs which is accompanied by nausea when exposed to deodorants, laundry detergents and bleach. Her past medical history includes multiple chemical sensitivity, pains all over

her body, OCD, panic attacks and anxiety disorder. This patient has recent exposure to carpet cleaner when she moved to a new apartment and this exaggerated her hyperosmia, anxiety , pain and a new onset burning tongue. The patient visited several clinicians and was prescribed vitamin supplements, therapies like exercise and meditation none of which improved her symptoms.

Results: Abnormal Examination: Cranial nerve examination- CN1- hyperosmia. Burning tongue- 0 in the early morning hours , 8- by the end of the day, lack of sleep exaggerates burning. Taste sensation - normal. Pain- in the joint areas. Neurological examination, MMSE, Cranial nerves examination, Motor examination, Sensory examination , Gait, Deep tendon reflexes, Neuropsychological testing and cerebellar examination are normal.

Discussion: The temporal correlation between multiple chemical sensitivity and hyperosmia strongly suggest that chemical induced decrease in GABA in the olfactory bulb is responsible for excess excitatory signals sent to the brain by Glutamate even at low thresholds of any substance. Also , decrease in the overall GABA is responsible for the pain experienced by this patient. In those with multiple chemical sensitivity investigations to detect the presence of hyperosmia is warranted. Further, clinical trials for the use of GABAergic medications in hyperosmia patients would be worthwhile.

153. Lateral Modified Brandt-Daroff Exercises (LMBDE): Introduction of a New Lateral Canal Benign Paroxysmal Positional Vertigo (BPPV) Treatment Maneuver Based on Simulation with a Biomechanical Model

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Objective: Lateral canalithiasis is the second most common variant of benign paroxysmal positional vertigo (BPPV), accounting for 3-30 of cases. Brandt-Daroff exercises have successfully been used for treatment of posterior canalithiasis, but their use for lateral canalithiasis has not been previously studied. Based on simulation with a biomechanical model, we investigated modifications of Brandt-Daroff Exercises which may optimize their use in the home treatment of lateral canalithiasis.

Methods: BPPV Viewer, a 3D biomechanical model of the human membranous labyrinth, was used to analyze Brandt-Daroff Exercises in the treatment of lateral canalithiasis. Using the model's gravity function, the expected position of otoliths was demonstrated while moving the model through sequential positions of the Brandt-Daroff Exercises. These steps were adjusted systematically to reveal the maximum otolith movement around the canal circumference that could be achieved without compromising repositioning otoliths into the anterior arm of the semicircular duct. All technique adjustments were integrated into Lateral Modified Brandt-Daroff Exercises (LMBDE) presented here.

Results: Brandt-Daroff Exercises can be used for home treatment of lateral canalithiasis by implementing several modifications. Simulation with our model indicates that tilting the head 20° upward in the lateral position, instead of 45° as specified by the original technique, significantly increases displacement of otoliths originating from the anterior and intermediate segments of the lateral duct. This can be performed as a direct two-step technique without the need to pause in the upright sitting position before switching sides. If the affected ear is known, positioning the head 45° below horizontal on the unaffected side as a third treatment step can promote actual lateral canal evacuation. These treatment enhancements increase the degree of otolith movement around the circumference of the canal and may promote lateral canal evacuation.

Conclusion: LMBDE are a modification of Brandt-Daroff Exercises that can increase their effectiveness for use in patients with lateral canalithiasis. Analysis with the 3D model predicts efficacy over standard Brandt-Daroff exercises for lateral canal BPPV; however, these results should be confirmed with controlled clinical patient analysis, which is currently being initiated at our institution. As lateral canalithiasis is the second most common cause of BPPV that may be left untreated with Brandt-Daroff Exercises, this modification may improve home treatment of this common condition, which is especially important in resource limited settings.

154. Neuroimaging in Zambian Children with HIV and New Onset Seizure: Findings from the CHASE Study

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Background: HIV in Sub-Saharan Africa (SSA) is a significant cause of morbidity and mortality despite widespread use of combination antiretroviral therapy (cART). Acute symptomatic seizures in children occur more often in SSA than in the West and epilepsy is a common HIV comorbidity. Although not routinely available in many SSA settings, neuroimaging in new onset seizures may offer insights into seizure etiology, HIV-associated pathophysiological effects, and risks of subsequent epilepsy. We report the imaging findings in the urban children in the Cohort of HIV-Associated Seizures and Epilepsy (CHASE) Study.

Methods: The CHASE Study is a prospective cohort study of HIV-infected individuals. From April 2016-April 2019, HIV-infected children evaluated at the University Teaching Hospital Children's Hospital in Lusaka, Zambia with new onset seizure were eligible for enrollment. Two neuroradiologists independently interpreted imaging using the NeuroInterp data capture program with adjudication by consensus. Clinical and demographic data were obtained including details of HIV disease and treatment, seizure etiology, and neurodevelopmental status (Malawi Developmental Assessment Tool [MDAT] and Universal Non-Verbal Intelligence Test [UNIT]). Children were followed quarterly for at least 1 year. The association between specific imaging findings (atrophy, focal structural lesions, subcortical white matter abnormalities, and leptomeningeal abnormalities) and HIV disease and outcomes (epilepsy, death) were examined using t-test or chi-square analyses.

Results: Among 49 enrolled children, 39 had imaging (54% male, mean age 6.8, 22% MRI). Advanced HIV disease was common with 49% of the children on cART and 36% with status epilepticus. Imaging findings included diffuse atrophy (49%), focal structural lesions (67%), subcortical white matter abnormalities (38%), subdural fluid collections (21%), vascular events (21%), and leptomeningeal abnormalities (23%). During follow-up, 38% of children died with 28% of deaths occurring during the index admission. Epilepsy developed in 33%. Atrophy was associated with more advanced HIV disease and severe neurocognitive impairment (p=0.02). Focal structural abnormalities were associated with greater seizure severity/status epilepticus (p=0.008). Focal structural abnormalities were NOT predictive of subsequent epilepsy, but were associated with death during the index admission.

Conclusion: In this study, imaging findings were diverse. Brain atrophy was associated with advanced HIV disease and neurocognitive disabilities. Focal structural lesions were associated with severe seizures at presentation and early death. In contrast to prospective studies in the West, focal lesions were not predictive of subsequent epilepsy, possibly due to the competing outcome of death.

155. A Translational Medicine Approach for Clinical Trial Readiness of Min-102 (Leriglitazone) in Neurodegenerative and Neuroinflammatory Disorders

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Objectives: To evaluate the pharmacokinetic parameters and disease-relevant biomarkers in plasma and CSF, relevant to the mechanism of action of leriglitazone for CNS disorders, after single and multiple oral administration in healthy male volunteers.

Background: Leriglitazone is a differentiated peroxisome proliferator-activated receptor γ (PPARγ) agonist with a superior profile for central nervous system (CNS) related diseases with excellent *in-vivo* efficacy. Non-clinical studies show antioxidant and neuroprotective effects, improvement of mitochondrial function, promotion of re-myelination and potent anti-inflammatory effects in several CNS models. in vivo plasma exposure derived from non-clinical efficacy and pharmacokinetic experiments were used to identify effective plasma and CSF concentrations in mice and supported the design of the Phase I study.

Design/Methods: A randomized, double-blind, placebo-controlled, single-centre clinical trial was conducted in 33 healthy male volunteers to investigate whether leriglitazone achieves the levels of plasma exposure and CNS penetration that were associated with efficacy in non-clinical models, and whether the effects on various biochemical markers of PPARϒ engagement and inflammation could be replicated in man. Single doses of 30 mg, 90 mg, and 270 mg and multiple doses of 135 mg/day and 270 mg/day were administered over 8 days. Plasma and CSF samples were collected to evaluate PK parameters and biomarker levels.

Results: Single and multiple doses of leriglitazone appeared to be safe and well tolerated, while plasma exposure more than 2 times above the required level for efficacy was achieved. CSF levels of leriglitazone confirmed CNS penetration sufficient for efficacy as indicated by non-clinical experiments. A decrease in plasma pro-inflammatory biomarkers (such as Interleukin-8, CXCL10-IP10 or MCP-1) and an increase of adiponectin levels in plasma and CSF were reported, confirming a high degree of PPARϒ engagement.

Conclusions: Tolerability, pharmacokinetic and pharmacodynamic results ensured trial readiness and de-risked efficacy studies in degenerative and inflammatory CNS disorders. Leriglitazone is currently in clinical phase 2/3 for the treatment of adrenomyeloneuropathy, an in phase 2 for cerebral adrenoleukodystrophy and Friedreich´s Ataxia.

156. Improvement of Cognitive Deficits and Neuronal Markers in HIV Associated Neurocognitive Disorder Mice Treated with Curcumin

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HIV associated neurocognitive disorders (HAND) affect approximately 50% of HIV-infected individuals regardless of whether they receive combined antiretroviral therapy (cART). Mild cognitive deficits predominate in cART HAND patients, but eventually lead to dementia, especially in an aging population of HIV-positive individuals receiving cART. Therefore, adjunctive therapies need to be developed. Here we utilize a mouse model of HAND that enables us to measure mild cognitive deficits before and after novel treatments are administered, which simulates important features of potential human trials for novel HAND therapies. Object recognition testing (ORT) demonstrated significant ($p< 0.001$) cognitive deficits in HAND mice injected intracerebrally with HIV-infected human monocyte derived macrophages (MDM) compared to control mice that are injected

with uninfected MDM. Curcumin was then administered subcutaneously qday 50 mg/kg to half of the HAND mice and the other half (n=8 for all groups) received saline. Repeat ORT after 1 week of treatment revealed significant cognitive improvement ($p< 0.045$) in HAND mice given curcumin compared to HAND mice given saline. We also are analyzing HAND (treated vs saline) and control mice pathologically, including mononuclear phagocyte (MP) and astrocytic responses, neuronal dendrite and receptor changes, and the potential relationship of dendritic simplification and decreased AMPA receptors (AMPAR) to decreases in β-catenin, a signaling molecule that has potential ties to dendritic and spiny process scaffolding. Preliminary data suggests that curcumin treatment reduces brain inflammatory profile (Class II positive) MPs and astrogliosis. This is consistent with previous reports showing an inhibitory effect of curcumin on MP inflammatory responses. Additional preliminary data utilizing flow cytometry of dissociated brains suggests a reduction in neuronal β-catenin in HAND brains. Data are also being analyzed on AMPAR expression in mouse brain tissue sections. We predict decreases in neuronal β-catenin will correlate with decreased neuronal surface AMPAR in HAND mice, which would probably be a reflection of destabilized scaffolding with resultant reduction of spiny process formation on dendrites. These pathological findings would be reflective of cognitive dysfunction in HAND mice. We further predict that curcumin treatment will correct neuronal pathology. Ultimately, treatments such as curcumin, which is widely available, may be applicable to HAND patients and in other cognitive disorders where dysregulated spiny process scaffolding and/or reduced AMPA receptors are involved in pathogenesis.

157. Variability of the Quantitative Neuroimaging Biomarkers

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Objective: Our objective is to measure the normal variations of the quantitative neuroimaging biomarkers and especially correlate it to the size of the region of interest (ROI). This will help us interpret a level of change in the biomarker as a real biological change or a normal variation.

Background: Quantitative neuroimaging biomarkers may be used to study normal brain or neurological diseases. The biomarker is conventionally the mean value of a parametric map within a ROI. In such case, the ROI size becomes important, as by increasing the size, the measurement will have a smaller variance. This is important in decision-making in the prospective clinical studies when the ROI size is variable, e.g., in monitoring the effect of treatment on lesions by quantitative MRI, and in particular when the ROI is small, e.g., in the case of brain lesions in multiple sclerosis. Thus, methods to estimate normal variations for arbitrary sizes of ROI are desired. Repeatability coefficient estimated by repeatability studies is representative of the normal variations and is studied here.

Methods: We describe the values of the parametric map within the ROI by a statistical model and propose a method to estimate the model parameters. We take into account the spatial dependence of the values of the parametric map using an exponential covariogram model. We use the parameters of the statistical model to estimate the repeatability coefficient for an ROI with an arbitrary size. Repeatability coefficient is used to determine the level of change due to measurement error and thus can be used to interpret the variations of measurement. Experiments are conducted on simulated data as well as on scan-rescan brain MRI of healthy subjects. Simulated data are generated by a set of model parameters. The parameters are then estimated and compared with the ground truth.

Results: We observed dependence of the repeatability coefficient on the ROI size in both real and simulated data. Higher variability was observed in smaller ROIs. Examples of small ROI study are voxel-wise analysis of brain imaging biomarkers and monitoring small lesions. The results show that the proposed method accurately estimates the repeatability coefficients.

Conclusion: Normal variations need to be correctly estimated based on the ROI size in studies with small ROIs. An important application of this study is the adjustment of the decision threshold based on the lesion size in the monitoring of treatment.

158. Global Prevalence of Tuberculosis in the Central Nervous System: A Systematic Review and Meta-Analysis

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Introduction: Tuberculosis (TB) is the first cause of death for a single infectious agent worldwide. Although the primary manifestation of TB is pulmonary, cases of extrapulmonary TB (EPTB) are not rare, representing 15% of all TB reported cases. Central nervous system tuberculosis (CNS TB) is one of the most challenging clinical diagnosis, and it is associated with high morbidity and mortality burden. Despite epidemiological data of TB, the worldwide prevalence of CNS TB remains unknown. This study aims to estimate the global prevalence of Central Nervous System (CNS) Tuberculosis (TB) based on available literature.

Methods: A systematic review of the literature was conducted in Medline, Cochrane Central, Scopus, and Lilacs databases from inception to April 2020. We included

observational epidemiological studies (cross-sectional, case-control, and cohorts) that evaluated the prevalence of CNS TB. Two independent researchers selected, assessed the quality of the studies, and extracted relevant data. We performed random-model effects meta-analysis of proportions to estimate the pooled prevalence worldwide. The protocol of this study was registered in PROSPERO (CRD 42018103946).

Results: We included 53 studies from 28 countries were included in the study. A total of 12621 patients with CNS TB were included. The prevalence of CNS TB was 1,12 (IC95%: 1,05-1,19) per 100'000 inhabitants. Based on subgroup analysis the prevalence for meningeal tuberculosis and tuberculoma were 1,16 (IC95%: 1,09-1,24) and 0,20 (IC95%: 0,05-0,46) per 100'000 inhabitants, respectively. The countries with more prevalence were Indonesia and Colombia; the countries with the lowest prevalence were Germany and Denmark. Most of the studies had a high risk of bias, mainly in the sampling method and case definition.

Conclusion: The prevalence of CNS TB was 1,12 per 100'000 inhabitants. The most frequent type was meningeal tuberculosis. The higher prevalence was reported in low and middle-income countries. The high risk of bias, heterogenicity of the studies, and potential data under registration could reduce the accuracy of our estimates. Population-based studies from low and middle-income countries are needed for a better estimation of the worldwide prevalence.

159. Characterization of HIV-Associated Neurocognitive Impairment in Older Persons with HIV in Lima, Peru

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With widespread use of antiretroviral medications, people with HIV (PWH) are living to geriatric ages worldwide, increasing the risk of developing neurocognitive impairment (NCI). The proportion of Peruvians over age 60 is expected to increase to 25% of the population by 2050. The problem of aging and dementia especially in HIV is pressing, however, prevalence of HIV-associated NCI in Peru remains unknown. We sought to determine the prevalence of and factors associated with NCI among older Peruvians with HIV. We recruited 144 PWH and 52 age- and education-matched HIV-negative controls ≥age 40 living in Lima, Peru from September 2019 to March 2020. Sociodemographic and medical comorbidity (infectious and chronic) data were collected. A brief neuropsychological battery and PHQ-9 for depression screening were administered; raw scores were adjusted for age, sex and education level. NCI was defined as impairment in ≥2 cognitive domains. T-test and logistic regression analyses were performed. Among PWH, mean age was 52+/-8 years and education achieved 14+/-3 years; 15% were female. Median (IQR) current CD4 and nadir CD4 was 554 (371, 723) and 179 (83, 291), respectively. Mean time since HIV diagnosis was 10+/- 7 years, 14% had detectable plasma viral load and all were on antiretrovirals. The prevalence of NCI was 20.8% among HIV+ group, including those with suppressed plasma viral loads (VL), and 23% among the control group; there was no significant difference in NCI prevalence between groups (p=0.73), but the HIV+ group demonstrated significantly more motor slowing (p=0.04). There was no difference in depression prevalence by history and PHQ-9, but a history of depression or PHQ-9 score ≥4 (mild depression or worse) predicted NCI (OR 3.67, 95% CI 1.6, 8.7) among the HIV+ group but not among the HIV- controls (OR 2.3 [0.61, 9.0]). No other medical/psychiatric comorbidity nor HIV characteristic (nadir and current CD4, current plasma VL) was predictive of NCI. NCI among older Peruvians with HIV was found to be prevalent, but there was no significant difference when compared to controls likely due to limitations of a possible self-selection bias in our control group and inability to sex-match. However, depression was associated with NCI among PWH but not among controls, despite similar rates of depression in both groups. This is the first step in generating awareness of the gap in dementia policies among those living with HIV in Peru.

160. Improving Tuberculous Meningitis Diagnostics: A Combined Host and Pathogen Classifier

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Objectives: To assess the diagnostic performance of metagenomic next-generation sequencing (mNGS) combined with host differential gene expression for tuberculous meningitis (TBM) versus other causes of meningitis.

Background: GeneXpert RIF/MTB Ultra is ~70% sensitive for definite/probable TBM. Definite TBM is microbiologically proven. Probable TBM has negative microbiology but scores >10 points on the case definition scale. 90-98% of mNGS sequencing data reflect host gene expression. Host transcriptomic signatures may differ by pathogen and thus, enhance diagnostic utility. We assessed CSF mNGS and transcriptomics for identifying TBM and other pathogens misclassified as TBM.

Cohort: 157 HIV-infected Ugandan adults with sub-acute meningitis: Definite (n=15), probable (n=7), and possible (n=53) TBM; non-TB meningitis (n=82).

Method: Unbiased RNA and DNA libraries were sequenced. We performed metagenomic analysis through a custom bioinformatics pipeline. Transcriptomic diagnostic classifier was developed using 22 samples (11 TB + 11 other), which, along with cases with co-infections, were not included in the final analysis.

Results: mNGS was 80% concordant (12/15) against definite TBM with 3 additional cases of TBM detected (1 probable and 2 possible). Host transcriptomics displayed 100% (6/6) sensitivity (inclusive of mNGS-positive TBM), 87% (67/77) specificity, with an Area Under the ROC Curve of 0.95 (0.90-1.0). Among probable TBM cases the host transcriptomic classifier predicted 71% (5/7) were TBM including the 1 mNGS-positive TBM case. Within possible TBM, mNGS identified 9 other pathogens (4 viral, 2 bacterial, 2 toxoplasmosis and 1 TBM-viral co-infection). The host transcriptomic signature classified 5/53 possible TBM cases as TBM, including the 1 mNGS-positive TBM case.

Conclusion: mNGS and host transcriptomics combined for 77% (17/22) sensitivity against definite/probable TBM. mNGS alone detected TB or alternate pathogens in 19% (10/53) of possible TBM cases. Further optimization of the classifier is required to increase accuracy. The combined assay will be assessed on a validation cohort of 207 cases with results presented at the meeting.

161. Improving Neuromuscular Disease Clinical Care and Research in Zambia

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Objective: We aim to describe a Nerve Conduction Study (NCS) training program for technicians in Zambia that can provide a framework to improve neuromuscular disease (NMD) diagnosis and research in Sub-Saharan Africa (SSA).

Background: There is a great lack of expertise and access to Nerve Conduction Studies and Needle electromyography (NCS/EMG), which is a major barrier to improving clinical care, epidemic surveillance, and NMD research in SSA. Since 2013, Michigan State University (MSU) and the University Teaching Hospital (UTH) in Lusaka, Zambia have collaborated to establish a NCS/EMG lab. This has facilitated NMD diagnosis for which disease modifying treatments are available on government formulary (Kvalsund, Journal of neurological Sciences 2019). Task shifting NCS performance to technicians would facilitate increased electrodiagnostic consultations and research capacity for NMDs in this setting.

Methods: We designed an Intensive 6 week training course for NCS technicians, undertaken at UTH, a large tertiary care center in Lusaka, Zambia. The course integrated prior experience with U.S. residency training and experience working with non-physician health care workers in Zambia. Course protocol was designed by Neurology and Physiatry residents, with the assistance of board certified NMD specialists and led the NCS course in Zambia. Course participants included two medical clerks and a licensed physiotherapist. First two weeks consisted of daily lectures on basic anatomy, electrophysiologic concepts, standardized performance of routine NCS of the upper and lower extremities, and hands-on practice among course participants. Weekly practical examinations were delivered by an NMD specialist assessing NCS knowledge and technique. Following successful completion of the practical exam, participants were allowed to begin working with clinical cases during weeks 3-6 under specialist and resident supervision.

Results: Challenges included varying baseline anatomy and computer knowledge among participants, environmental/electrical artifact interference, and clinical schedule adjustments to allow sufficient time for trainees to complete NCS on clinical cases. Five months after the course all participants continue to conduct weekly NCS with varying degrees of independence and have gained proficiency beyond routine studies.

Conclusion: Six week NCS training courses can provide a solid foundation for skill acquisition among participants of varying levels of post-secondary education in resource-limited settings. Task shifting for electromyography will be more challenging but must be considered to truly expand access to the test regionally.

162. When to Test Primary Neurologic Patients for Covid-19 Infection

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Introduction: Patients with Covid-19 have been found to present with neurologic manifestations prior to or even without manifestation of typical symptoms. These patients may not be considered as potential Covid-19 patients as they may present without fever, chills, or shortness of breath. This may subsequently place patients and staff at risk for preventable exposure and, therefore, knowledge on this subject area should be expanded with further studies and retrospective reviews. Guidelines should be implemented in respective hospital facilities to guide healthcare providers on when to test a patient presenting for new or worsening neurologic symptoms that may be related to infection with 2019-nCoV. Resources for testing are limited and placing a patient under investigation for 2019-nCoV infection requires use of limited personal protective equipment, increases the patient burden on already overwhelmed staff, and places the patient under stringent precautions and isolation. Therefore, selection of patients for testing should be carefully considered.

Methods: Literature review pertaining to pathophysiology, presentation of, and neurologic complications of 2019-nCoV was performed and combined with first hand clinical experience in Covid-19 patients with neurologic symptoms.

Findings: Patients with new or worsening neurologic symptoms that cannot otherwise be explained by underlying mechanisms should be considered for testing. In our hospital

of mainly Hispanic patients, presentations and sequelae of Covid-19 have included new onset generalized seizures, large vessel occlusions, encephalopathy, headache, and others in a wide array of patients with and without cardiovascular or neurologic risk factors. These presentations may occur in patients with no previous history of neurologic disease or in patients with pre-existing neurologic disease.

Discussion and Conclusion: We propose an algorithm to help clinicians determine atypical testing candidates for COVID-19 as well as what risk factors need to be identified, what lab values should be considered, and what limitations are posed along with mitigation strategies. Further studies should be preformed to assess for statistical significant of neurologic symptoms in Covid-19 patients.

163. Familial Influenza Associated Acute Necrotizing Encephalopathy

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Introduction: Influenza is a viral pathogen that imposes an under-recognized burden of central nervous system (CNS) disease. While mostly diagnosed in the pediatric population, neurological complications of pandemic influenza A infection may affect young and previously healthy adults, and may follow a fulminant, severe, and occasionally fatal course.

Case Description: We presented 2 cases of influenza-associated encephalopathy (IAE) that happened in a family after influenza A infection.

Case 1: The father is a 42-year-old man with a PMH of HTN only who presented to the ED for 5 days of headache with associated fever/chills and vomiting. His mental status quickly deteriorated after admission with no focal neurological deficits. He was positive for influenza A. Lumbar puncture revealed elevated CSF protein level but negative meningitis panel. His MRI brain w/wo demonstrated T2 hyperintensities with DWI restriction within bilateral thalami, subinsula and hippocampus. Patient was empirically treated with acyclovir, oseltamivir and high-dose steroids. On hospitalization day 12, the patient was safe to discharge to home.

Case 2: Several days after his father's admission, the son, a healthy 9-year-old boy, presented to the ED, with fever, rhinorrhea, headache, and sore throat along with nausea, vomiting, and abdominal pain. He was diagnosed with influenza A and was discharged to home with oseltamivir in ED. His nausea worsened, which quickly evolved to confusion and visual hallucinations. He then developed bradycardia and hypoxia. Patient was admitted to the pediatric ICU. His MRI demonstrated similar findings. He received methylprednisolone and IVIG, along with other supportive management. On hospitalization day 14, he was discharged to home.

Conclusion: Influenza-associated acute encephalopathy (IAE) is an uncommon but serious complication with high mortality and neurological sequelae. We presented here a rare familial case series of IAE. The exact etiology of this condition is still under investigation but likely associates with the "cytokine storm" that caused multiorgan failure. One other member of the family also contracted influenza but did not develop encephalopathy. Steroids, IVIG, plasmapheresis have all been used to treat this condition in the literature. Unfortunately, because of the rarity of the IAE, there is no established treatment guideline so far. Interestingly, the clinical picture of IAE share a certain similarity with that of the recently identified severe COVID19 cases. The ongoing clinical trials of tacrolimus and steroid for the COVID19 patients may shine some light on the treatment of IAE.

164. Community Acquired Meningitis from Serratia Marcescens in an Adult: A Case Report

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Objective: To describe the first case of spontaneous Serratia marcescens monoinfection in CSF in an adult with intravenous drug abuse.

Background: Gram negative rods are an uncommon cause for meningitis. A rise in nosocomial gram negative bacillary meningitis has been observed. Serratia is a described pathogen for acute cerebrospinal fluid (CSF) infections in neonates and iatrogenic cases.

Results: We report this case of a 53 year old male with active intravenous drug use (IVDU) and no previous neurosurgical procedures, who presented with altered mental status and gait instability for 2 weeks along with headache, nausea and vomiting for 2 months. CT scan revealed hydrocephalus requiring urgent placement of an intraventricular catheter. Initial CSF analysis revealed glucose of <10mg/dl, protein of 107mg/dl, WBC count of 67cells/mm^3, and RBC count of 125cells/mm3. Three separate CSF cultures drawn at 48 hour intervals each grew Serratia marcescens. Metagenomic next generation sequencing from CSF confirmed the presence of Serratia without any co-infection. MRI of the cervical spine was concerning for C1-C2 septic arthritis for which he underwent surgery but cultures were negative. Blood cultures remained negative throughout. Patient received intravenous antibiotics that improved his clinical condition. Intrathecal gentamycin was later added for continued inflammation in CSF, which then resolved.

Conclusion: Serratia marcescens is an extremely rare cause of acute meningitis in adults and reported cases have a history of cranial, spinal or otic manipulation. On the contrary, our patient had an insidious onset of meningitis resulting in hydrocephalus with no prior procedures. His IVDU was likely a risk factor, though there was no evidence of bacteremia. Atypical organisms in CSF can often be disregarded as contaminants. This can delay therapy and increase morbidity and mortality. Our case highlights an atypical presentation of meningitis caused by a rare organism.

165. Syphilitic Meningitis in Lusaka, Zambia

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Objective: Determine the prevalence of syphilitic meningitis (SM) among adults presenting with features of meningitis to the national referral hospital in Lusaka, Zambia and compare their clinical features, demographic characteristics and outcomes to adults with other central nervous system (CNS) infections.

Background: SM is one form of neurosyphilis, a severe manifestation of syphilis affecting the CNS. Although the incidence and prevalence of neurosyphilis is increasing in much of the world, little is known about its epidemiology in sub-Saharan Africa.

Design/Methods: We analyzed serum and cerebrospinal fluid (CSF) samples collected during a prospective cohort study of adults presenting with features of meningitis to the University Teaching Hospital between April 2014 and December 2017. Serum samples were tested for syphilis using treponemal pallidum haemagglutination (TPHA) tests. In samples that were TPHA-positive (TPHA+), the corresponding CSF was tested with venereal diseases research lab (VDRL) tests. CSF white blood cell (WBC) count, protein, *Mycobacterium tuberculosis* (TB) culture, and TB PCR were completed as part of the parent study which also collected clinical, demographic and outcome data of participants. SM was defined according to the Centers for Disease Control diagnostic criteria for neurosyphilis: serum TPHA+ and CSF VDRL+ and/or elevated protein and/or CSF pleocytosis in the absence of alternative CNS infection. Comparisons were made between individuals with SM and those without.

Results: Of 512 participants, 273 were male, mean age was 37 + 11 years, and 88.5% were HIV+. Fifty (10%) participants were serum TPHA+. Twenty-four (5%) met criteria for SM, of which 22 were HIV+ (96%). Glasgow Coma Scale score was lower in participants with SM [median (IQR): 11 (8, 14)] than for those with other infections [14 (11, 15), p=0.02], but clinical symptoms were not significantly different between the two groups. Participants with SM had higher median CSF WBC [10 (0, 30) vs 0 (0, 8), p=0.02) and protein [g/L: 0.91 (0.67, 1.97) vs 0.54 (0.30, 1.56), p=0.01]. Overall, there was no difference in in-hospital mortality, and 1-year mortality was 53% for both groups.

Conclusion: The prevalence of SM among adults with meningitis in Zambia is higher than previously reported in the region, and one-year mortality is high. Clinicians in sub-Saharan Africa need to strongly consider SM in the differential of meningitis. Interventions are needed to improve diagnosis and treatment of SM to improve outcomes.

166. "Doctor Myself": Barriers to Effective Diagnosis and Treatment of Zambians with Meningitis

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Background: Adult Zambians with meningitis present late to hospitals and little is known about community understanding of meningitis or treatment sought before hospitalization. The Meningitis Cascade of Care study is examining barriers to meningitis care in Lusaka, Zambia.

Methods: In-depth interviews are ongoing with patients admitted with meningitis, their caregivers, doctors, and nurses at the University Teaching Hospital (UTH). Patient/caregiver interviews address prior illness experiences, meningitis treatment, and understanding of biomedical care. Provider interviews focus on prior clinical experiences, care of a current meningitis patient, and inpatient care challenges. A framework approach was used to assess barriers that may increase mortality.

Results: Of 82 eligible patients (68% male; 76% HIV+), 18 patients (67% male, 83% HIV+) or their caregivers have been interviewed. One caregiver had heard of meningitis; 4/18 said meningitis was equivalent to cerebral malaria. 10/18 patients first reported severe headache; 11/18 thought symptoms were from malaria. Patients tried, on average, three self-care actions before UTH referral. 9/18 patients first went to a local clinic. Of those that did not, reasons for clinic avoidance included overcrowding and concern that recommended treatment at local clinics would be equivalent to self-care; 7/9 patients used over-the-counter medications, two tried prayers. Severe symptoms (obtunded, seizures, or hallucinations) were the impetus for biomedical care. 10/18 patients were seen by outpatient clinic staff multiple times before inpatient referral. All patients and caregivers had heard of lumbar puncture (LP) and 16/18 stated that it is a dangerous procedure that can cause death. 15/18 had an inpatient LP recommended, 6/15 patients/caregivers refused. During admission, patients/caregivers described difficulty understanding the patients' illness and paying for requested tests. 3/18 died. Four nurses and one physician have been interviewed (80% female). All reported that patients and families rarely understand their illness and refuse LP due to fear of death. Nurses had difficulty simplifying explanations about the patient's illness and reported that high patient loads limited patient/family education.

Conclusions: Awareness of meningitis as a distinct condition is low among patients and caregivers. Among those

interviewed, headache and fever were often attributed to malaria and patients pursued conservative treatment until severe symptoms developed. Patient/caregiver limited understanding of disease, confusion with cerebral malaria, and fear of LP may hinder treatment-seeking behavior. This is compounded further by health system barriers at the clinic level.

167. Palliative Care Needs amongst Stroke Patients in Zambia

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Background: Stroke is the second leading cause of death and disability worldwide. Most strokes occur in low- and middle-income countries where acute interventions are rare, and mortality is often higher than in high-income countries. In the absence of rehabilitation systems and skilled nursing facilities, patients are often transitioned to home-based care upon discharge. Little is known about palliative care needs of stroke patients in sub-Saharan Africa.

Objective: Determine the proportion of Zambians with stroke with unmet palliative care needs and elicit the most common specific needs.

Methods: We conducted a cross-sectional study of all adults with stroke admitted to the neurology inpatient service at the University Teaching Hospital in Lusaka, Zambia. All participants completed the Palliative Outcome Scale (POS), a survey of 10 multiple choice questions regarding symptom management, and two open-ended questions eliciting problems over the past three days and concerns about the transition home after discharge. Where patients were unable to communicate, caregivers were surveyed. Individuals with POS score > 20 met criteria for unmet palliative care needs.

Results: We surveyed 125 participants, 76 (61%) female with median age 61 (interquartile range 47-70) and 15 (13%) with HIV infection. 39% of participants had unmet palliative care needs, most commonly personal/practical problems that were not addressed, pain, family/friends anxious about their condition, feeling poorly about themselves as a person, and feeling as though time was wasted on healthcare. When asked about their most significant problems over the three days prior to the survey, 34% reported difficulty with mobility, 29% an inability to talk, and 26% unilateral weakness. An additional 19% reported headache and 18% other uncontrolled pain. The most common concerns regarding transitioning home were around mobility (46%), general ability to provide care at home (29%), financial resources to buy medications and supplies (26%), the patient's potential for recovery (21%), and toileting (17%).

Conclusions: In this low-resourced setting with high stroke burden in which all stroke patients are cared for at home upon discharge, 39% of stroke patients were discharged with unmet palliative care needs. Further work is needed to improve post-discharge transitions to home in order to address patient-reported concerns and, possibly, reduce post-discharge mortality in low-resourced settings like Zambia. Efforts to develop palliative care services are also imperative in these settings in order to address this substantial unmet need.

K-590. Folate Deficiency Is Associated With Distal Symmetric Polyneuropathy In Zambian Clinics

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Introduction: Low serum vitamin B12 and folate levels were recently found in 60% of Zambian HIV+ and HIV- persons with distal symmetric polyneuropathy (DSP), but the population prevalence of these deficiencies are unknown. We sought to estimate the risk of vitamin B12 and folate deficiency among DSP cases compared to age (+/- 5 years), sex, HIV, and clinic-matched controls recruited from four urban and one peri-urban government clinics in Zambia.

Methods: DSP diagnosis was based on having at least one symptom and at least one sign consistent with DSP, as determined by a physician using the Brief Peripheral Neuropathy Scale and Utah Early Peripheral Neuropathy Scale. HIV negative controls were identified among persons present at the health clinics, but not seeking personal medical care. HIV positive controls were persons seeking antiretroviral medication refills without a medical complaint. All participants underwent full blood count, renal and liver profiles, and biomarkers for vitamin B12 and folate. HIV testing and CD4 counts were performed when appropriate. Participants were interviewed regarding sociodemographic, medical, dietary and nutritional supplementation history.

Results: Among 107 consenting case-control pairs, participants were 65% female, 52% HIV positive, and had a mean age of 47.5 (SD 13.5) years. Among HIV positive participants, mean CD4 count was 474 (SD 212) and 473 (SD 230) for cases and controls, respectively (p=0.93). DSP symptoms and severity did not differ between HIV positive and HIV negative cases (p's>0.05). Height, prior tuberculosis treatment, alcohol use, education, asset index, dietary diversity, and nutritional supplement use did not differ between cases and controls (p's>0.05). DSP cases had ≥ 3:1 odds of having low serum folate (p=0.002), severely low erythrocyte folate (p=0.014), and elevated homocysteine (p=0.001) levels compared to controls. Low or suboptimal vitamin B12 and elevated methylmalonic acid concentrations were found in >30% of study participants, but were not associated with case status (all p's>0.05).

Conclusions: Markers of folate deficiency are highly associated with DSP in government clinic attendees in Zambia, suggesting either undernutrition or under-absorption of folate may be driving high DSP rates in this setting. Further studies should establish if nutritional neuropathies are also prevalent outside of clinical settings. Additional studies should also investigate the risk of other nutritional neurologic morbidity as well as the role of a broader range of nutritional deficiencies and strategies for interventions.

K-597. **Elevations In Complement During S. Epidermidis Cerebrospinal Fluid Shunt Infection**

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Cerebrospinal fluid (CSF) shunt infection is a common and devastating complication of the treatment of hydrocephalus. The majority of these infections are cause by *S. epidermidis* and can lead to long term neurologic consequences such as seizures, decreased IQ and impaired school performance. The mechanisms by which these consequences occur are unknown. Our preliminary studies in a rat model of CSF revealed elevated levels of many complement components at late time points when bacterial burdens were low suggesting a role for complement beyond bacterial opsonization. Complement has been associated with the pathogenesis of neurodegenerative diseases such as MS and Alzheimer's as well as CNS infections such as HIV and bacterial meningitis. More recently there is evidence to support the role of complement components in directing developmentally appropriate synaptic pruning. This literature and our preliminary proteome studies suggest that complement may be responsible, in part for the neurologic damage that occurs in response to CSF shunt infection. We hypothesize that complement creates these deleterious neurologic effects through pathologic pruning of neural synapses. To evaluate this hypothesis we used a standardized mouse model of *S. epidermidis* CNS catheter infections, allowing for the evaluation of host response to infection. Early data demonstrated elevated levels of the complement components C3 and C5 at days 5 and 10 post-infection, when bacterial burdens are low again suggesting a role beyond control of the infection. Additional studies comparing WT and C3 KO mice demonstrate a trend towards increased synaptic number in C3 KO mice compared to WT which supports our hypothesis that complement is responsible for pathologic synaptic pruning in *S. epidermidis* shunt infection. Should our hypothesis prove to be correct we could take advantage of the many complement inhibitors in development and improve patient outcomes.

Headache and Pain

208. Increased Headache Prevalence in Patients with Chronic Neuropathic Pain

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Neuropathic pain is defined as pain from peripheral neuropathy that has features of allodynia, paresthesia, burning, tingling, pins and needle sensations. Small fiber neuropathy (SFN) is a common cause of these neuropathic symptoms. Many patients with chronic neuropathic pain (CNP, neuropathic pain > 6 months) frequently complain of headaches. In this study, we examined the correlation between CNP and chronic headaches by reviewing the medical records of Massachusetts General Hospital (MGH) from 2018-2020. Two hundred and seventy-four medical records from patients who had skin biopsies for evaluation of neuropathic symptoms are included in this study. Among these patients (80 males and 194 females), the prevalence risk of CNP is 45%. Twenty five percent of CNP patients have chronic headache with a majority (69%) of these cases are diagnosed with chronic migraine. Gender preference is significant with females consist of 90 % of subjects with migraine and CNP. All these patients underwent skin biopsy on distal legs to measure the intraepidermal nerve fiber densities (IENFD) at MGH. Our results demonstrate 59% of patients who have a positive skin biopsy vs 39% of patients have negative skin biopsy have CNP, supporting CNP is associated with reduced IENFD. However, the prevalence risks of chronic headache and migraine are not significant different between the two groups. In summary, our result demonstrated the increasing prevalence of chronic headache, especially chronic migraine, among female patients with CNP. This association is not related to the diagnosis of SFN using skin biopsy.

209. Utilizing Telemedicine in an Interdisciplinary Academic Headache Center

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While the coronavirus pandemic interrupted the ability of our interdisciplinary headache center to conduct in-person visits, it also enabled our team, consisting of headache neurology, occupational and physical therapy, and pain psychology, to utilize a telemedicine platform to evaluate and treat patients. Prior to the pandemic, our patient, a 32-year-old female with a history of chronic daily headaches and occipital neuralgia, was receiving monthly in-person visits with each team member.

Headache Neurology: Intervention prior to the pandemic included magnesium infusions and unsuccessful trials of nortriptyline, amitriptyline, topiramate, gabapentin, escitalopram, oral magnesium, and oral riboflavin. Given the delays in magnesium infusions during the pandemic, oxytocin is being trialed and is currently being uptitrated.

Pain Psychology: The patient was diagnosed with Generalized Anxiety Disorder. She was aware that "stress" (i.e., negative self-talk about stressors and resulting sympathetic activation) triggered, worsened, and maintained her headaches and neck pain. Although the telehealth visit precluded the possibility of providing electromyogram and temperature biofeedback, it allowed for seamless delivery of cognitive behavioral therapy (cognitive restructuring of fearful or depressing thoughts about her headaches) and guided imagery for stress management.

Occupational Therapy: Prior to the pandemic, the patient reported a busy schedule of work and social activities. She identified as a "people pleaser" and reported difficulty

"saying no" to events and activities. During her OT telehealth appointment, patient reported overexertion in areas such as home management, screen time, and avocation. Strategies for integrating activity pacing was identified as being relevant and beneficial during shelter-in-place and transition back to work. This helped her understand the relationship between overexertion and migraine.

Physical Therapy: The patient previously identified time constraint barriers that inhibited her ability to incorporate exercise routines into her weekly schedule. She was also reluctant to perform exercises because she did not experience benefits from exercises in the past. Bi-weekly PT telehealth visits provided the opportunity to help the patient establish a daily exercise routine that she felt confident performing in her home environment. Exercises have focused on improving postural habits and increasing strength of postural muscles. By continuing healthcare services through a telehealth platform, the patient has been able to make ongoing strides in learning and implementing self-care strategies to improve self-efficacy in managing her migraines and neck pain. She has implemented activity-pacing strategies, incorporated stress management strategies, and now identifies exercise and movement as beneficial to manage pain.

210. Triggers of Status Migrainosus and Higher Morbidity Amongst Migraineurs

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Introduction: Status migrainosus (SM) affects <1% of migraineurs with the duration of >72 hours and resistant to standard migraine medicines, responsible for migraine hospitalizations. A large observational data might help to identify triggers of SM among patients with migraine.

Aim: We tried to find out the prevalence trend of SM, assessed the risk factors to identify the triggers and morbidity predictors for SM.

Methods: We performed a population-based retrospective cross-sectional analysis of Nationwide Inpatient Sample (years 2003-2014) in adult (>18-years) hospitalizations for status migrainosus (and intractable migraine) using ICD-9-CM code. Morbidity was defined by hospital stay >5-days (>90 percentile of mean migraine hospitalizations) and discharge other than home(short-term hospitals/skilled nursing facility/home health care/intermediate care facility). We performed a weighted univariate analysis using the chi-square test, paired t-test, and the Cochran-Armitage trend test. We performed a weighted multivariate survey logistic regression analyses to evaluate the triggers of SM and predictors of SM-related morbidity.

Results: A total of 446,446 US hospitalizations had a primary diagnosis of migraine. Out of these, 130,914 (29.32%) patients had SM. There was a significant increase in the prevalence of SM in the migraineurs (2003:27.49% to 2014:32.68%; pTrend<0.0001). Patients with SM tend to be younger (mean age 41-year vs.45-year), females (85.86% vs. 78.31%; p<0.0001), and whites (81.83% vs. 70.31; p<0.0001), compared to patients without SM. On weighted analysis, drug abuse (4.76% vs. 3.93%; aOR=1.13; 95% CI=1.03-1.24), vitamin D deficiency (0.70% vs. 0.53%; aOR=1.28; 95%CI=1.05-1.56), opioid abuse (1.76% vs. 0.99%; aOR=1.43; 95%CI=1.22-1.68), organic sleep disorder (3.41% vs. 3.06%; aOR=1.38; 95%CI=1.26-1.50), medication overuse headache (1.66% vs. 0.28%; aOR=3.63; 95%CI=2.95-4.45), generalized anxiety disorder (1.36% vs. 0.63%; aOR=1.50; 95%CI=1.28-1.77), major depression disorder (29.03% vs. 19.26%; aOR=1.56; 95%CI=1.50-1.62), and post-traumatic stress disorder (1.90% vs. 1.21%; aOR=1.37; 95%CI=1.21-1.55) were associated with higher prevalence and odds of SM. SM patients had higher prevalence and odds of morbidity (1.20% vs. 0.98%; aOR=1.67; 95%CI=1.43-1.96) in compared to patients without SM. Acute ischemic stroke (aOR=2.60; 95%CI=1.34-5.07), hemorrhagic stroke (aOR=7.07; 95%CI=1.94-25.72), obesity (aOR=1.47; 95%CI=1.22-1.78), atrial fibrillation (aOR=1.62; 95%CI=1.19-2.20), renal failure (acute/chronic/end-stage) (aOR=1.38; 95%CI=1.04-1.83), epilepsy (aOR=2.31; 95% CI=1.88-2.82), generalized anxiety disorder (aOR=1.78; 95% CI=1.02-3.11), major depression disorder (aOR=1.38; 95% CI=1.19-1.61), and post-traumatic stress disorder (aOR= 1.74;95%CI=1.15-2.66) were associated with higher morbidity in SM patients.

Conclusion: We have identified important triggers of SM from the risk factors of migraine. Early identification and management of triggers mitigate the burden of SM.

211. CGRP Monoclonal Antibodies: Targeted Migraine Treatment and Cardiovascular Safety Profile

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Migraines headaches are a common complaint for patients and they can be difficult to effectively manage. Few medication options have been developed to specifically target the pathogenesis of migraines. The available treatment options have been associated with numerous side effects, specifically cardiovascular complications. More recently, calcitonin gene related peptide (CGRP) monoclonal antibodies were developed to target a specific component of the molecular pathway contributing to migraines. The targeted pathway is initiated by inflammation which stimulates the release of various neuropeptides, such as CGRP, and causes vasodilation. Sensory fibers within the trigeminal nerve then perceive the vasodilation as pain. Therefore, blocking CGRP was hypothesized as a possible target for migraine treatment. Initially, there was concern that blocking the vasodilatory process of migraines may exacerbate cardiovascular disease. This is an important correlation to assess because patient's with migraines have been shown to be at greater cardiovascular and cerebrovascular risk. CGRP has been shown have many protective effects

on the cardiovascular system by preventing against heart failure, deleterious cardiac remodeling, hypertension, and cell death. A review of this topic compiled research articles relating to CGRP, migraines, and cardiovascular risk. The articles were analyzed for data on the efficacy of eptinezumab, erenumab, galcanezumab, and fremanezumab, the four medications in this class. These studies were further analyzed for adverse reactions and cardiovascular events. Specifically, studies with high female participation were evaluated to determine safety and efficacy of the CGRP monoclonal antibodies in this target population, as they are those most commonly affected with migraines. Research has shown that all medications in the class decrease the number of migraine headache days per month, when compared to placebo. The most common adverse events that occurred after use of the medication were upper respiratory tract infection, sinusitis, nasopharyngitis, back pain, and fatigue. Cardiovascular adverse events occurred at similar rates in patients taking the medication and placebo. This demonstrated that the medications do not increase risk of cardiovascular side effects. These results were also consistent for patients with preexisting cardiovascular conditions. This medication class was shown to be safe and effective for migraine treatment in females and caused no cardiovascular side effects. The studies mentioned above demonstrated cardiovascular safety in high risk and targeted patient populations. Future studies on long term cardiovascular safety with use of this medication class may be warranted.

212. Distinct Clinical Features of Red Ear Syndrome in Pediatric Population

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Background: Red Ear Syndrome (RES), a rare disorder, is characterized by unilateral or bilateral redness of external ear with pain and burning sensation. The prevalence, classification, pathophysiology and treatment of RES are yet undefined. Previous authors had suggested idiopathic (primary) RES and RES secondary to other causes. Early-onset idiopathic RES seems associated with migraine whereas late-onset idiopathic form have been reported in association with trigeminal autonomic cephalagias.

Methods: We presented an adolescent case of RES and reviewed the literature from 1996 to 2019 to clarify different clinical presentations of RES between pediatric population and adult cases.

Results: A 16-year-old man presented with intermittent redness and burning sensation in both ears. Symptoms usually lasted for about 20-30 minutes and resolved spontaneously. Neurological exam is completely normal. We reviewed reported cases of RES from 1996 to 2019. Total 26 pediatric cases and 68 adult cases were included. 24/26 pediatric RES cases were male (92%) but majority cases in adult group were female (51/68; 75%). 16/26 (62%) in pediatric RES vs. 9/68 (13%) in adult cases had bilateral symptoms. 19/26 (73%) pediatric case reported history of headache whereas less than half (29/68; 43%) adult cases had history of headache. Only 3 cases reported in pediatric RES with secondary cause but 30/68 (44%) adult cases were found to be caused by certain neurological condition such as upper cervical pathology or temporomandibular joints dysfunction. The duration of each attack ranged from seconds to several days. Most cases in pediatric group had symptoms lasted less than 60 minutes.

Conclusion: RES is a relatively newly described condition first reported by Lance in 1996. It was thought to be a rare disorder but this condition maybe overlooked, and the incidence is underestimated. Our review showed that close to one third of the reported RES cases occurred in pediatric population. Clinical manifestations in pediatric population differed from adult cases in that they occurred almost exclusively in male with predominantly bilateral involvement, shorter duration and rarely associated with secondary causes, which may indicate a different disease entity or pathogenesis in those patients. Raieli reported that RES is not uncommon in juvenile headache and seem to be highly specific to migraine. Lambru has proposed diagnostic criteria for primary RES in his review article in 2013. Based on our review, a different diagnostic criteria may need to be applied in pediatric population.

213. Case Report: Transient Global Amnesia in a Child

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Background: Transient Global Amnesia (TGA) is a short-lived clinical syndrome characterized by confusion and memory loss in the absence of other focal neurologic deficits. The amnesia is self-limited, anterograde, lasting for fewer than 24 hours; with variable retrograde involvement. Patients often describe a precipitating event, such as an emotional stressor or physical exertion. Though numerous pathophysiological mechanisms have been proposed, including vascular/ischemic and epileptic processes, a definite etiology has not been found. Of note, migraines have been associated with an increased risk of TGA, suggesting a possible shared mechanism. TGA is most frequently encountered in patients above 50 years of age, but the condition is rare in pediatric populations. We report a rare case of TGA in an 11-year-old.

Case Presentation: An 11-year-old male with a past medical history of ADHD and anxiety presented to the emergency department (ED) with a new-onset of confusion and repetitive questioning. The patient and family reported numerous recent stressors, but denied any recent trauma, illness, or ingestion. There is a family history of migraine in the sibling. Comprehensive metabolic panel was normal except for a mild increase in liver transaminases. His vital signs were within normal limits. During hospitalization, the patient was awake and oriented but was noted to be agitated and uncooperative, which needed to be treated with Ativan and Benadryl. He also had nausea treated with Zofran and a headache treated with Toradol. Apart from poor short-term memory recall and agitation, no other focal neurological deficits were present.

On investigation, CT and MRI of the head were normal. Prolonged EEG did not reveal any signs of slowing or epileptiform activity. Around 17 hours after onset of symptoms, the patient returned to baseline with a normal neurologic exam. A diagnosis of transient global amnesia was made by the Pediatric Neurologist. At discharge, migraine prophylaxis was recommended if such events become recurrent, but counseled that TGA is a self-limited condition.

Conclusion: The signs and symptoms of TGA mimic other conditions, such as transient ischemic attack/cerebrovascular accident, seizure, complex migraine, intoxication, or conversion disorder. As the majority of children affected by TGA will present to the ED or to a Primary Care Provider, it is essential that providers recognize TGA as a potential differential diagnosis for a child presenting with new-onset confusion/amnesia after excluding more sinister diagnoses.

214. Outcomes of Patients Presenting with Headaches Hospitalized with COVID-19

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Although headaches are a well-characterized symptom of coronavirus disease 2019 (COVID-19) infection, limited data exists comparing the clinical course of such hospitalized patients who initially present with headaches to those who do not. This retrospective observational study analyzed outcomes of patients aged ≥18 years with laboratory confirmed COVID-19 infection admitted to the Mount Sinai Health System between February 27 and April 19, 2020. Patients presenting with headaches, identified by Natural Language Processing (NLP) analysis of intake notes, were propensity score-matched (5:1) by age, gender, race/ethnicity, comorbidities, and body mass index (BMI) to patients who did not present with headaches. Baseline clinical characteristics, admission symptoms, laboratory values collected within 48 hours of admission, and clinical outcomes were compared between the two groups. Univariate statistical significance was identified with Kruskal-Wallis one-way ANOVA or chi-squared tests at Bonferroni-adjusted P<0.05 (multiplying P by 66 study-wide tests). During the study period, 191 patients presenting with headaches were admitted and matched to 955 non-headache patients from the same study period. Patients were well-matched on age, sex, race/ethnicity, comorbidities, and BMI. Patients presenting with headaches had significantly higher rates of GI symptoms upon admission (nausea/vomiting, diarrhea) than non-headache patients (29% vs 18%, P < 0.01), as well as other neurological symptoms (impaired consciousness, dizziness) (17% vs 11%, P = 0.01). Patients with headaches had significantly lower levels of inflammatory markers upon admission, including C-reactive protein (P = 0.04), lactate dehydrogenase (P < 0.01), and procalcitonin (P = 0.01) than those without headaches. The subset of patients with headaches also had significantly lower white blood cell counts upon admission than patients without headaches (6200 vs 7300, P < 0.01). Patients presenting with headaches had similar levels of mortality, intubation, ICU admission, length of stay, and ventilator usage as patients who did not present with headaches. In this propensity score-matched analysis, hospitalized COVID-19 patients with headaches presented more often with concurrent neurological and GI symptoms but had similar levels of in-hospital mortality as patients without headaches.

215. Efficacy and Safety of AXS-07 (MoSEIC™ Meloxicam/Rizatriptan) in the Acute Treatment of Migraine: Results from the INTERCEPT Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: The objective of this study was to evaluate the efficacy and safety of early migraine treatment with AXS-07 versus placebo.

Background: AXS-07 (MoSEIC™ meloxicam/rizatriptan) is a novel, oral, rapidly absorbed, multi-mechanistic investigational medicine for the acute treatment of migraine. AXS-07 is thought to act by inhibiting CGRP release, reversing CGRP-mediated vasodilation, and inhibiting neuro-inflammation, pain signal transmission, and central sensitization. Axsome's MoSEIC™ technology significantly increases the speed of absorption of the meloxicam component while maintaining a long plasma half-life.

Methods: INTERCEPT was a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of AXS-07 in the acute early treatment of migraine. Eligible patients were randomized (1:1) to receive a single dose of AXS-07 or placebo and instructed to self-administer treatment at the earliest sign of pain, while mild. The co-primary endpoints were freedom from pain and from most bothersome symptom (MBS) at 2 hours post-dosing, for AXS-07 versus placebo.

Results: AXS-07 met both co-primary endpoints demonstrating a statistically significantly greater percentage of patients versus placebo achieving pain freedom (32.6% versus 16.3%, p=0.002) and freedom from MBS (43.9% versus 26.7%, p=0.003), 2 hours post-dosing. AXS-07 rapidly eliminated migraine pain, with numerical separation from placebo as early as 30 minutes, achieving statistical significance at 90 minutes (p=0.003) and every timepoint thereafter. A single dose of AXS-07 significantly prevented pain progression beyond mild intensity and significantly reduced rescue medication use. Freedom from pain progression from 2 to 24 hours after dosing was achieved by 73.5% of AXS-07 patients versus 47.4% of placebo patients (p<0.001). Only 15.3% of AXS-07 patients required rescue medication through 24 hours versus 42.2% of placebo patients (p<0.001). AXS-07 significantly reduced functional disability, with 73.5% of patients reporting no disability at 24 hours compared to 47.4% of placebo patients (p<0.001). AXS-07 was safe and well tolerated. The most commonly reported

adverse events with AXS-07 were somnolence, dizziness, and paresthesia, all occurring at rates less than 5%.

Conclusions: AXS-07 is a novel, oral, rapidly absorbed, multi-mechanistic investigational medicine for the acute treatment of migraine. In the INTERCEPT trial, early treatment with AXS-07 substantially and significantly eliminated migraine pain, and substantially and significantly prevented progression of migraine pain beyond mild intensity, as compared to placebo.

216. Migraine and Functional Impairment Associated with Driving: Results of the OVERCOME Study

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Objective: Characterize driving behaviors in people with migraine from the ObserVational survey of the Epidemiology, tReatment and Care Of MigrainE (OVERCOME) study.

Background: Migraine is associated with substantial functional burden, yet little is known about migraine-related driving impairment.

Design/Methods: OVERCOME is a web-based survey conducted in a representative US sample. The sample collected in Spring 2019 assessed the impact of migraine on driving frequency, duration of driving avoidance during headache, and days with an inability to drive. Monthly headache days (MHDs), MIDAS score, headache pain, and attack-related disability were assessed. Differences between categorical variables were assessed with Chi-square statistics and correlations were assessed with Spearman's rho (r).

Results: Among 5485 eligible participants with migraine and valid driver's licenses, mean (SD) age was 49.7 (14.2) and mean MHDs was 5.9 (7.0); 13.2% had chronic migraine. Mean MIDAS score was 14.3 (26.1); 19.5% had severe MIDAS disability. As pain intensity increased, the proportion reporting not driving with headache increased from mild (27.1%) to moderate (38.4%) to severe (66.0%) pain ($p<0.0001$ vs mild for both). Duration of driving avoidance increased with increasing MIDAS grade ($r= 0.39$), attack-related disability ($r=0.39$), and MHDs ($r=0.18$; $p<0.0001$ for all). The proportion of patients with ≥7 hours of driving avoidance increased with disability from moderate (26.6%) to severe (37.1%) to very severe (52.1%) ($p<0.001$). Among patients whose working ability was severely impaired or who required bed rest, 25.4% and 42.9% reported ≥7 hours of driving avoidance during attacks. Days with inability to drive in the past 90 days increased as migraine-related disability and MHDs increased ($p<0.001$).

Conclusion: An increasing proportion of people with migraine avoid driving as pain intensity increases, reaching 66% for those with severe pain. Driving avoidance lasting ≥7 hours occurs in almost half of those with severe disability. The impact of migraine on driving merits additional attention and clinical assessment.

217. Stigmatizing Attitudes Towards People with Migraine by People without Migraine: Results of the Overcome Study (2017-6229-005)

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Objective: People with migraine may experience stigma. Our objective was to evaluate stigmatizing attitudes towards people with migraine by people without migraine.

Design and Setting: Data were obtained in Fall 2018 from a web-based survey conducted in a representative US sample [ObserVational survey of the Epidemiology, tReatment and Care Of MigrainE (OVERCOME)].

Subjects: The sample included 2,000 respondents without migraine who were randomly selected to answer questions about attitudes towards people with migraine.

Outcome Measures: 11 attitudinal questions about migraine were posed to respondents. Questions were developed from qualitative research (focus groups/expert opinion) and answers scored on a 6-point Likert scale: [sometimes/often/very often] coded as YES and [don't know/rarely/never] as NO. We examined respondents' answers along two dimensions of proximity to migraine: familiarity of relationship (none, coworker, friend, family) and count of people they knew with migraine (0, 1, 2+).

Results: Sample mean age was 48; 51% were female and 65% were white. 45% of respondents reported that they knew no one with migraine, 5% knew a co-worker only, 37% knew one person (family/friend), and 13% knew multiple people with migraine. Overall, 33% (>45% among those knowing someone with migraine) endorsed, YES, that people with migraine use migraine to avoid school/work/family/social commitments. 32% (>40% among those knowing someone with migraine) endorsed, YES, that those with migraine exaggerate their symptoms.

Conclusion: Among respondents without migraine who knew someone with migraine, > 40% endorsed the idea that people with migraine use their disease to avoid activities and/or exaggerate their symptoms. The more people that respondents knew with migraine, the higher the likelihood of respondents holding stigmatizing attitudes. These findings may be explained by people without migraine experiencing the burden of migraine as stigma by association.

218. A Close Association of Pain Freedom with Freedom from Most Bothersome Symptom and from Migraine-Related Functional Disability in Lasmiditan Studies Samurai and Spartan

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Background: Lasmiditan is a selective 5-hydroxytryptamine 1F receptor agonist for the acute treatment of migraine.

Lasmiditan has been shown to be superior to placebo on freedom from pain and freedom from most-bothersome symptom (MBS) in 2 Phase 3 studies, SAMURAI (NCT02439320) and SPARTAN (NCT02605174).

Methods: This post-hoc analysis assessed whether the outcomes of pain freedom (reduction in pain severity from moderate or severe at baseline to none) or mild pain (reduction in pain severity from moderate or severe at baseline to mild were associated with the outcomes of MBS freedom or functional disability freedom in 2 hour pooled data from SAMURAI and SPARTAN (modified intent-to-treat population with moderate or severe pain, MBS and functional disability recorded at time of dosing). MBS freedom is defined as absence of the self-identified MBS [either nausea, phonophobia or photophobia]. Patients who recorded no symptoms present at time of dosing were excluded from the analysis. Functional disability was assessed with the question "How much is your migraine interfering with your normal activities." Response options were "not at all" (functional disability freedom), "mild interference," "marked interference," "need complete bed rest." Patients who recorded "Not at all" at time of dosing were excluded from the analysis. Patients treated with lasmiditan 200 mg with MBS and functional disability recorded at the time of dosing were assessed at 2 hours postdose. The coexistence of MBS freedom and functional disability freedom was examined in patients with pain freedom or mild pain.

Results: Patients with pain freedom (N=324) frequently also experienced MBS freedom (91.4%) and functional disability freedom (81.8%). In contrast, patients who experienced mild pain (N=220) showed lower rates of MBS freedom (45.0%; p=<0.001) and functional disability freedom (12.7%; p=<0.001) than pain-free patients In addition, more patients who were pain free experienced both MBS freedom and functional disability freedom (78.7%) compared to those with mild pain (10.0%; p=<0.001). Furthermore, 5.6% of patients experienced pain freedom without achieving MBS freedom or functional disability freedom compared with 52.3% of patients who experienced mild pain alone.

Conclusions: Achieving pain freedom with lasmiditan was frequently associated with MBS freedom and a return to normal activities.

219. Efficacy and Safety of AXS-07 (MoSEIC™ Meloxicam/Rizatriptan) in the Acute Treatment of Migraine: Results from the MOMENTUM Phase 3, Randomized, Double-Blind, Active- and Placebo-Controlled Trial

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Objectives: To evaluate the efficacy and safety of AXS-07 versus rizatriptan, MoSEIC™ meloxicam and placebo in the acute treatment of migraine in patients with a history of inadequate response to prior treatments.

Background: The WHO classifies severe migraine attacks as among the most disabling illnesses. Over 70% of patients are not fully satisfied with current treatments. AXS-07 is a novel, oral, multi-mechanistic, investigational medicine under development for the acute treatment of migraine. AXS-07 consists of MoSEIC™ meloxicam and rizatriptan. AXS-07 is thought to act by inhibiting CGRP release, reversing CGRP-mediated vasodilation, and inhibiting neuro-inflammation, pain signal transmission, and central sensitization. Axsome's MoSEIC™ technology significantly increases the speed of absorption of meloxicam, a potent, COX-2 preferential non-steroidal anti-inflammatory drug, with a long half-life (~20 hours).

Methods: MOMENTUM was a Phase 3, randomized, double-blind, placebo- and active-controlled study to assess the efficacy and safety of AXS-07 in the acute treatment of migraine. Eligible patients had to have a history of inadequate response to prior acute treatments, assessed using the Migraine Treatment Optimization Questionnaire. A total of 1,594 patients were randomized (2:2:2:1) to receive a single dose of AXS-07, rizatriptan, MoSEIC™ meloxicam, or placebo to treat a migraine attack with headache pain of moderate or severe intensity. The co-primary endpoints were freedom from migraine pain and from most bothersome symptom (MBS) two hours post-dosing, versus placebo. Superiority over rizatriptan and MoSEIC™ meloxicam was assessed based on sustained pain freedom.

Results: AXS-07 achieved the co-primary endpoints with statistically significant improvements versus placebo on freedom from pain (19.9% vs. 6.7%, p<0.001) and from MBS (36.9% vs. 24.4%, p=0.002) 2 hours post-dosing. AXS-07 demonstrated superiority to rizatriptan and MoSEIC™ meloxicam on sustained pain freedom (16.1% vs. 11.2%, p=0.038, and 8.8%, p=0.001, respectively). AXS-07 provided rapid pain relief, demonstrating numerically greater relief than rizatriptan at all timepoints with statistical significance by 60 minutes post-dosing (p=0.04). A significantly lower proportion of patients used rescue medication with AXS-07 versus rizatriptan, meloxicam, and placebo (23.0% vs 34.7%, 35.1%, and 43.5%, respectively, p<0.001 for each group). AXS-07 was safe and well-tolerated.

Conclusion: AXS-07 produced rapid, sustained, substantial and significant efficacy versus rizatriptan, MoSEIC™ meloxicam and placebo in the acute treatment of migraine in patients with a history of inadequate response.

220. Efficacy of Galcanezumab in Patients Who Had Not Benefited From Commonly Prescribed Migraine Preventive Treatments

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Objective: Evaluate the efficacy of galcanezumab in patients for whom commonly prescribed migraine preventives failed due to lack of efficacy or safety/tolerability.

Methods: Patients from a phase 3 study with a 3-month double-blind period (CONQUER) who had 2-4 migraine prevention medication category failures in the past 10 years were randomized 1:1 to receive placebo (N=230; PBO) or galcanezumab 120mg/month (240mg loading dose; N=232). GMB Post-hoc analysis was conducted to determine the

efficacy of galcanezumab in patients who had not benefited from different commonly prescribed migraine preventives. For the five most commonly failed preventives, the mean change from baseline in monthly migraine headache days over months 1-3 for galcanezumab compared to placebo was assessed by mixed model with repeated measures.

Results: In this population, the most commonly failed preventives included: topiramate (76.0%, N=351), amitriptyline (56.1%, N=259), propranolol (35.7%, N=165), valproic acid (34.9%, N=161), and onabotulinum toxin A (22.9%, N=106). The most common reasons for treatment failure were lack of efficacy followed by safety/tolerability. Patients who discontinued topiramate ($p<0.0001$; PBO, n=130; GMB, n=133), amitriptyline ($p<0.01$; PBO, n=104; GMB, n=103), propranolol ($p<0.05$; PBO, n=67; GMB, n=64), valproic acid ($p<0.01$; PBO, n=58; GMB, n=62) or onabotulinum toxin A ($p<0.01$; PBO, n=42; GMB, n=49) due to lack of efficacy had a significant reduction in monthly migraine headache days when treated with galcanezumab compared to placebo. Patients who discontinued topiramate ($p<0.05$; PBO, n=52; GMB, n=43) or amitriptyline ($p<0.05$; PBO, n=30; GMB, n=38) due to safety/tolerability had a significant reduction in monthly migraine headache days when treated with galcanezumab compared to placebo. There was a numerical reduction in monthly migraine headache days in patients who discontinued propranolol or valproic acid due to safety/tolerability reasons, but results were not statistically significant, likely due to the small number of patients in these subgroups (propranolol, PBO, n=8; GMB, n=18; valproic, PBO, n=19; GMB, n=19). Only one patient discontinued onabotulinum toxin A due to safety/tolerability reasons.

Conclusion: The most commonly failed prior preventive therapies in CONQUER are similar to what has been reported in past surveys. Galcanezumab was effective in reducing monthly migraine headache days in patients who had not previously benefited from topiramate, amitriptyline, propranolol, valproic acid, or onabotulinum toxin A due to lack of efficacy. It was also effective in those who had not previously benefited from topiramate or amitriptyline due to safety/tolerability.

221. Adverse Event Profiles of Therapies That Target the Calcitonin Gene-Related Peptide (CGRP) Pathway, During the First Six Months after Launch: A Real-World Data Analysis Using the FDA Adverse Events Reporting System (FAERS)

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Introduction: In 2018, three medications that target the calcitonin gene-related peptide (CGRP) pathway received FDA approval for the preventive treatment of migraine: erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm. The real-world adverse event (AE) profile of CGRP pathway-targeted migraine preventive treatments was evaluated using post-marketing data.

Methods: This retrospective analysis evaluated AEs spontaneously reported to the FDA during the first 6 months post-approval for patients treated with erenumab, fremanezumab, and galcanezumab. Data were obtained from FAERS, the FDA's database for safety surveillance. We evaluated cases in which the product was classified as the "primary suspect" associated with a reported AE. Reporting rates (RR) were calculated by dividing number of events in each AE category by estimated number of exposed subjects based on de-identified prescription data (IQVIA database) and multiplied by 1,000 to create a rate per 1,000 exposed. AEs were ranked based on frequency for each product.

Results: The top ten RRs per 1,000 were as follows: erenumab: wrong technique (4.97), constipation (4.90), migraine (4.89), accidental product exposure (4.83), drug ineffective (3.68), headache (3.32), injection-site pain (2.94), nausea (2.94), under-dose (2.55), and fatigue (2.33); fremanezumab: headache (1.27), drug ineffective (1.14), migraine (1.01), nausea (0.91), injection-site pain (0.81), pruritus (0.73), injection-site erythema (0.71), injection-site pruritus (0.63), injection-site rash (0.63), injection-site swelling (0.58); and galcanezumab: injection-site pain (4.90), under-dose (3.86), headache (3.07), migraine (2.99), drug ineffective (1.69), injection-site erythema (1.58), injection-site swelling (1.25); injection-site pruritus (1.14), nausea (1.09), and product-dose omission (1.09).

Conclusions: Migraine, headache, or drug ineffective AEs were commonly reported for all three products, as were migraine-associated symptoms and injection-site reactions. Constipation ranked second for erenumab but did not make the top ten AEs for fremanezumab or galcanezumab. Cardiovascular events were not ranked in the top ten for any of the products.

222. Narrative Review of Risk Factors and the Burden of Medication Overuse Headache on Quality-of-Life, Disability Outcomes, and Comorbidities

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Introduction: Medication overuse headache (MOH) is a common and disabling disease. The aim of this literature review was to assess MOH burden on quality of life (QoL), disability outcomes, and comorbidities.

Methods: This comprehensive review was conducted using published studies from September 5, 2014 to September 5, 2019. The search strategy was executed in the PubMed database using the keywords "medication overuse headache." Reference lists were screened and titles and abstracts were reviewed for relevance. Full-text copies for relevant, English-language articles were fully reviewed.

Results: Of 89 reviewed studies, 23 (26%) contained data on MOH-associated patient burden and disability. Evidence from the literature suggests a higher risk of developing MOH with analgesic and opioid use versus other treatments and that acute MOH is more likely in triptan, opioid, and barbiturate users but less likely in non-steroidal anti-inflammatory drug users. Risk of cognitive decline was higher in patients with chronic migraine (CM) regardless of MOH status, but patients with MOH were at higher risk of memory and executive dysfunction than patients without MOH. Depression and anxiety were more likely to occur in patients with MOH than in healthy patients, and have been shown to affect up to one-quarter of patients with MOH. One study found that, for 6 out of 8 items on the World Health Organization QoL Questionnaire, average scores were significantly lower in patients with MOH than in patients with migraine. A majority of individuals with MOH in the general population had grade IV (severe disability) scores on the Migraine Disability Assessment (MIDAS). Several studies found that, of patients with headache disorders (migraine, tension-type headache, or MOH), patients with MOH or probable MOH had the highest per-person disability estimates. Even after intervention, patients with MOH still had significantly worse disability scores than healthy patients. In addition, sleep quality was significantly worse for CM patients with MOH and a higher proportion were in the highest stress quintile compared with patients with CM without MOH.

Conclusion: This literature review showed that MOH is more likely with certain medications and is associated with a negative impact on patient's QoL and comorbidities. The results summarized here add to the growing body of knowledge on the burden of MOH and highlight the need to adequately address MOH in order to reduce the burden in migraine patients.

223. Efficacy of Fremanezumab in Subjects with Migraine and Prior Inadequate Response to Valproic Acid, Topiramate, or Onabotulinumtoxina in the Open-Label Period of the International, Multicenter, Randomized, Placebo-Controlled FOCUS Study

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Introduction: In the double-blind period (DBP) of the FOCUS study, fremanezumab demonstrated efficacy as a preventive treatment in subjects with episodic or chronic migraine (EM/CM) and documented inadequate response to 2-4 prior migraine preventive medication classes. In the open-label extension (OLE), efficacy in subjects with inadequate response to valproic acid (VPA), topiramate, or onabotulinumtoxinA was evaluated.

Methods: This phase 3b study included a 12-week DBP and 12-week OLE. In the DBP, subjects were randomized (1:1:1) to subcutaneous (SC) quarterly fremanezumab (months 1/2/3: 675mg/placebo/placebo), monthly fremanezumab (months 1/2/3: 675mg[CM], 225mg [EM]/225mg/225mg), or matched placebo. After completing the DBP, subjects entered the OLE and received monthly fremanezumab (225mg) for 3 months. During the OLE, changes from baseline (BL) in monthly average migraine days (MMDs) in subjects with prior inadequate response to valproic acid (VPA), topiramate, or onabotulinumtoxinA and ≥1 other prior migraine preventive medication class were evaluated and compared by double-blind randomization group (DB group).

Results: Of 838 subjects randomized, 807 entered the OLE. Among subjects with prior inadequate response to VPA (n=247) and VPA and 2-3 other preventive medication classes (n=157), subjects experienced reductions from BL in MMDs over the 12-week OLE (mean [standard deviation (SD)]: VPA, DB quarterly fremanezumab, −4.4 [4.69]; DB monthly fremanezumab, −5.4 [5.40]; DB placebo, −4.1 [5.14]; VPA and 2-3 other medication classes, −3.9 [4.94], −6.0 [4.78], and −4.2 [4.86], respectively). The proportion of subjects with prior inadequate response to VPA and 2-3 other preventive medication classes achieving ≥50% reduction in MMDs was higher in both fremanezumab DB groups (quarterly, 44%; monthly, 47%) than the placebo DB group (29%). Mean (SD) changes from BL in MMDs in the DB quarterly fremanezumab, monthly fremanezumab, and placebo groups were −5.2 (4.77), −5.1 (4.94), and −4.8 (5.66), respectively, among subjects with prior inadequate response to topiramate (n=590) and were −4.0 (5.39), −4.5 (4.63), and −3.9 (4.89), respectively, among subjects with prior inadequate response to onabotulinumtoxinA (n=218). Similar reductions in MMDs had been observed in these groups with DB fremanezumab treatment.

Conclusions: Treatment with fremanezumab over up to 6 months (DBP and OLE) was effective in providing sustained reductions in MMDs.

224. Long-Term Efficacy of Fremanezumab in Patients with Episodic Migraine and Chronic Migraine Who Failed at Least One Prior Migraine Preventive Medication: Results from 6- and 12-Month Studies

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Introduction: Fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), has demonstrated efficacy for preventive treatment of episodic migraine (EM) and chronic migraine (CM). This analysis evaluated efficacy outcomes for fremanezumab in patients with EM or CM and inadequate response to ≥1 prior migraine preventive medication in a 1-year extension of the 3-month HALO studies or inadequate

response to 2-4 prior migraine preventive medication classes in the open-label extension (OLE) period of the FOCUS study.

Methods: In the 1-year extension study (LTS), quarterly or monthly fremanezumab treatment was maintained; patients who previously received placebo were randomized 1:1 to quarterly or monthly fremanezumab. In the FOCUS OLE, all patients completing the 3-month, double-blind period (DBP) entered the OLE and received 3 monthly doses of fremanezumab (225mg). Efficacy outcomes included changes from baseline in monthly average number of migraine days (MMDs) and headache days of at least moderate severity (HDs) and proportion of patients responding with ≥50% reduction in MMDs.

Results: Of 1890 patients enrolled in the 1-year LTS, 700 had inadequate response to ≥1 preventive medication. In the FOCUS study, 559 patients with documented inadequate response to 2-4 classes of prior preventive treatment were randomized to fremanezumab in the DBP, and 543 continued receiving fremanezumab in the OLE. Fremanezumab treatment for 6 to 12 months resulted in the following mean reductions in MMDs: LTS, CM quarterly fremanezumab, −6.4; LTS, CM monthly fremanezumab, −7.1; LTS, EM quarterly fremanezumab, −5.1; LTS, EM monthly fremanezumab, −5.2; FOCUS, CM/EM quarterly fremanezumab, −5.1; FOCUS, CM/EM monthly fremanezumab, −5.5. Similarly, fremanezumab treatment resulted in the following mean reductions in HDs: LTS, CM quarterly fremanezumab, −6.1; LTS, CM monthly fremanezumab, −6.9; LTS, EM quarterly fremanezumab, −4.5; LTS, EM monthly fremanezumab, −4.3; FOCUS, CM/EM quarterly fremanezumab, −4.8; FOCUS, CM/EM monthly fremanezumab, −5.2. Approximately half or more of patients achieved clinically meaningful (≥50%) reduction in the MMDs (LTS, CM quarterly fremanezumab, 48%; LTS, CM monthly fremanezumab, 51%; LTS, EM quarterly fremanezumab, 59%; LTS, EM monthly fremanezumab; FOCUS, CM/EM quarterly fremanezumab, 45%; FOCUS, CM/EM monthly fremanezumab 46%).

Conclusion: Across multiple study populations with inadequate response to prior treatment, fremanezumab was efficacious up to 6 months (FOCUS DBP and OLE) or up to 15 months (3-month HALO studies and 1-year LTS).

225. Pooled Analysis of Safety and Tolerability with Fremanezumab Treatment in Patients with Migraine and Baseline Cardiovascular Medication or Concomitant Triptan Use

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Introduction: Fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), has proven efficacy for preventive treatment of migraine in adults. Safety and tolerability were evaluated in subgroups of episodic or chronic migraine (EM or CM) patients: with cardiovascular (CV) medication use at baseline or with and without concomitant triptan use (given the frequency of triptan use in migraine patients).

Methods: This analysis included data from three phase 3 trials (HALO EM, HALO CM, and FOCUS), in which EM or CM patients were randomized 1:1:1 to subcutaneous quarterly or monthly fremanezumab or matched placebo over 12 weeks. Adverse events (AEs) of all types were evaluated for patients with CV medication use at baseline. CVAEs were evaluated for patients with and without triptan use.

Results: Overall, 280 of 2,842 patients across these 3 studies were receiving CV medications (eg, renin-angiotensin system agents, beta-blockers) at baseline, with similar proportions receiving CV medications across all treatment groups (9-11%). Among patients receiving CV medications at baseline, the most common AEs were injection-site-related pain (placebo, 19%; quarterly fremanezumab, 29%; monthly fremanezumab, 20%), erythema (10%, 20%, and 13%, respectively), and induration (8%, 18%, and 24%, respectively). Cardiac disorder AEs were infrequent across all treatment groups (placebo, <1%; quarterly fremanezumab, 0%; monthly fremanezumab, 1%), as were vascular disorder AEs (0%, 1%, and 3%, respectively). Additionally, 1,123 (40%) of the total pooled population (N=2,842), used triptans during the studies, with similar proportions using triptans across all treatment groups. Of patients with triptan use, 19 (2%) of patients experienced ≥1 CVAE, with no difference between patients receiving placebo (2%) and those receiving fremanezumab (quarterly, 2%; monthly 2%). Occurrences of all CVAEs were consistently low across all treatment groups; the only CVAE with >1 occurrence in the placebo and fremanezumab groups was hypertension. The incidence of CVAEs was low and similar in patients without triptan use (n=1,719; 46 [3%]). Among patients without triptan use, CVAEs with >1 occurrence in any treatment group were palpitations, hypertension, hematoma and hot flush, and all were reported in ≤1% of patients. No safety signals were identified.

Conclusion: This pooled analysis demonstrates that fremanezumab treatment over 12 weeks was safe and well tolerated in patients with migraine with baseline CV medication use and with and without concomitant triptan use.

226. Efficacy of Fremanezumab in Patients with Migraine and Documented Inadequate Response to 3 or 4 Migraine Preventive Medication Classes and Medication Overuse in the International, Multicenter, Randomized, Placebo-Controlled FOCUS Study

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Introduction: Fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), has demonstrated efficacy as a preventive treatment in patients with episodic migraine

(EM) or chronic migraine (CM) and documented inadequate response to 2-4 prior migraine preventive medication classes in the FOCUS study. The primary endpoint (change from baseline in monthly average migraine days [MMDs]) for the FOCUS study was evaluated in different subgroups of patients with difficult-to-treat migraine.

Methods: During the 12-week, double-blind period, patients were randomized (1:1:1) to quarterly fremanezumab (Months 1/2/3: 675mg/placebo/placebo), monthly fremanezumab (Months 1/2/3: 675mg[CM], 225mg [EM]/225mg/225mg), or matched placebo. Changes from baseline in MMDs were evaluated in subgroups with inadequate response to ≥3 migraine preventive medication classes, inadequate response to ≥4 medication classes, inadequate response to ≥3 medication classes and acute medication overuse at baseline, and inadequate response to ≥3 medication classes and ≥8 days of acute medication use at baseline.

Results: Of 838 patients randomized, 420 had inadequate response to ≥3 medication classes, 155 had inadequate response to ≥4 medication classes, 229 had inadequate response to ≥3 medication classes and acute medication overuse at baseline, and 327 had inadequate response to ≥3 medication classes and ≥8 days of acute medication use at baseline. MMDs were significantly reduced with fremanezumab vs placebo in the overall FOCUS population (difference in the change from baseline [95% confidence interval]: quarterly vs placebo, −3.1[−3.84, −2.42] and monthly vs placebo, −3.5[−4.19, −2.78]). Reductions in MMDs were comparable or greater than in the overall population in subgroups with inadequate response to ≥3 classes (quarterly vs placebo, −3.5[−4.62, −2.38] and monthly vs placebo, −3.6[−4.70, −2.56]), inadequate response to ≥4 medication classes (quarterly vs placebo, −4.5[−6.58, −2.37] and monthly vs placebo, −5.3[−7.30, −3.29]), inadequate response to ≥3 classes and overuse of acute medication (quarterly vs placebo, −2.7[−4.93, −0.56] and monthly vs placebo, −3.7 [−5.56, −1.78]), and inadequate response to ≥3 classes and ≥8 days of acute medication use (quarterly vs placebo, −3.5 [−4.92, −2.00] and monthly vs placebo, −4.3[−5.68, −3.01]).

Conclusion: In patients with difficult-to-treat migraine, including inadequate response to ≥3 and ≥4 medication classes and overuse of acute medication, fremanezumab treatment resulted in substantial reductions in MMDs, comparable to the overall FOCUS population.

227. Depression and Migraine - A Double Whammy on Patient-Reported Health

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Introduction: Depression is a common comorbidity in patients with migraine. Differences between patient-reported health in patients with and without depression who had chronic and episodic migraine (CM and EM) could offer insight into treatment of these migraine subgroups. We therefore examined any differences that may exist between these subgroups in a large tertiary headache clinic.

Methods: We performed a retrospective observational cohort study of patients >18 years of age with a primary or secondary encounter diagnosis of EM or CM seen in the Cleveland Clinic Headache Clinic between January 2012 and June 2017. Patient-reported outcome (PRO) measures included the European Quality of Life 5-dimensions (EQ-5D), PROMIS Global Health (GH), Pain Disability Index (PDI), Headache Impact Test-6 (HIT-6), and the Patient Health Questionnaire-9 (PHQ-9). PRO scores were compared between study participants with and without depression stratified by migraine subtype. The first PRO score completed during the study period was used in this analysis.

Results: PROs were available for 4,336 (91.1%) CM patients and 5,603 (89.3%) EM patients. Patients with CM had worse self-reported health on all PROs compared to EM patients (all P values <0.001). Patients with CM were more frequently diagnosed with depression (48.2%) than EM patients (31.6%; P<0.001). Within each migraine subtype, patients with depression had significantly worse PRO scores than patients without depression. Among CM patients, mean (standard deviation [SD]) PRO scores for those with and without depression were: EQ-5D = 0.58 (0.23) vs 0.69 (0.21); PROMIS GH Physical Health = 37.8 (7.6) vs 40.8 (7.1); PROMIS GH Mental Health = 38.5 (8.9) vs 44.0 (8.8); PDI = 37.3 (17.4) vs 29.1 (17.8); HIT-6 = 68.2 (6.8) vs 66.4 (6.1); PHQ-9 = 13.4 (6.4) vs 9.1 (5.9), all P <0.001. Although overall scores were better in EM patients, differences in mean scores between patients with and without depression for each PRO were similar between the CM and EM subgroups.

Conclusions: Depression is prevalent in patients with migraine and was documented in almost one-half of patients with CM and one-third of those with EM. Migraine patients with depression had significantly worse self-reported health as assessed by multiple patient-reported scales spanning different health constructs; the degree of worsening was similar between chronic and episodic migraine patients. Attention to the management of comorbid depression in migraine patients could have a marked impact on quality of life for many migraine sufferers.

228. A Real-World Perspective on the Characteristics of Migraine Patients Prescribed Ajovy, Emgality, or Aimovig in the United States

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Introduction: Fremanezumab (Ajovy®), erenumab (Aimovig®) and galcanezumab (Emgality®) are recently approved calcitonin gene-related peptide pathway-targeted treatments (anti-CGRPs) for adults with chronic migraine (CM) or episodic migraine (EM). This study assessed patient

characteristics and clinician treatment utilizations among the anti-CGRPs.

Methods: Data were obtained from the Veradigm Health Insights Database. The study period was January 1, 2014-June 30, 2019. Patients were included if they had ≥1 migraine diagnosis encounter during the study period, a medication record indicating initiation of any anti-CGRP on or after the initial diagnosis date during the identification period (September 1, 2018-June 30, 2019; anti-CGRP prescription date=index date) and were aged ≥18 years on the index date. All study variables were examined descriptively.

Results: Overall,15,207 patients were included (AJOVY, N=3,716; Emgality, N=2,569; Aimovig, N=8,922), of which most were female (85.8%) and had EM (62.3%). Of 3,716 patients prescribed AJOVY, 2,222(60%) had EM, 1,299 (35%) had CM, 2(<1%) had persistent migraine, and 193 (5%) had both EM and CM. Baseline demographics were similar across the EM and CM cohorts. The most common comorbidities were depression (666[18%]) and anxiety (715[19%]), with a significant difference in prevalence of anxiety disorders between the EM and CM cohorts (20% vs 17%; $P<0.05$). Mean(SD) age was similar between the AJOVY and Aimovig groups (47.21[13.03] and 47.68 [13.23]), but Emgality patients (45.96[12.93]) were significantly younger than AJOVY patients ($P=0.0002$). During the 12 months before the index date (baseline period [BP]), significantly greater proportions of Emgality and Aimovig patients, respectively, versus AJOVY patients used migraine-specific acute medications (56.1% and 51.9% vs 49.6%) and had comorbid depression (23.7% and 19.8% vs 17.9%; $P\leq0.0225$). While patients prescribed Emgality had a significantly greater mean(SD) number of migraine preventive prescriptions versus patients prescribed AJOVY during the BP (3.78[4.22] vs 3.55[4.21]; $P=0.0359$), patients prescribed Aimovig used a comparable number of preventive prescriptions (3.47[4.00]) to those prescribed AJOVY ($P=0.2727$).

Conclusion: In both EM and CM groups, patients who were prescribed AJOVY were largely women and approximately 47 years of age. While patients prescribed AJOVY, Emgality, and Aimovig shared some similar baseline characteristics, there were several significant differences when comparing clinical features. These results may contribute to understanding prescribing differences for these anti-CGRPs and further optimize patient care for migraine.

229. Changing Perceptions of Interdisciplinary Care for Headache Patients via Telehealth during Covid Pandemic

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A comprehensive treatment approach with an interdisciplinary team comprised of physical therapy, occupational therapy, pain psychologist, and headache specialist, can be very effective in improving disability due to headache disorders. However, patient factors including traveling distance and multiple appointments can be limiting factors to team care. The model of care at USC headache center with 4 headache specialists working with a headache team, shifted to an entirely telehealth-based delivery due to Covid-19 Pandemic. During 2 months (April-May 2020), Telehealth visits by all members of the care team were necessitated by stay-at-home orders and social distancing guidelines, and 451 telehealth visits were done for headache patients by occupational therapists (OTs) and physical therapists(PTs) as part of their comprehensive headache management. At the beginning of the pandemic, there were concerns by all members of the team, including some preconceived notions regarding the limitations of examination and treatment in a virtual treatment platform. However, the telehealth platform emerged as an especially useful platform for the delivery of interdisciplinary team care. Using a telehealth platform, OTs were able to visually evaluate patients directly in their home or work environments, rather than a clinical environment which allows for only verbal discussion. Occupational therapists evaluate functional abilities and contextual and environmental factors that impact the performance of headache patients. Physical therapists were able to utilize movement observation along with subjective reports in a telehealth platform, to infer likely source of musculoskeletal impairments contributing to headache and provide patients with self-mobilization, self-massage, or exercise to manage musculoskeletal symptoms and headache. PT telehealth is an opportunity to observe patients in their home environment, which allows for real-time problem solving about modifications and engage patients in exercise routines while they are at home. Patients were overall very satisfied with telehealth evaluations and showed improvements that paralleled in-person visits, and in some cases were better than traditional methods of care delivery. In conclusion, changing perceptions regarding the utility of Telehealth for delivery of team care both among patients and providers in headache medicine include a surprisingly better understanding of patient factors affecting headaches, improved access to multiple healthcare providers, easier scheduling, and coordination and compliance with treatment plans. Telehealth may be a long-term tool that can be utilized for headache patients to improve delivery of team-based care.

230. Efficacy of Fremanezumab in Migraine Patients with Medication Overuse and Documented Inadequate Response to 2-4 Migraine Preventive Medication Classes: Subgroup Analysis of the Randomized, Placebo-Controlled FOCUS Study

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Introduction: The FOCUS study of fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), was the first and largest study of a migraine preventive treatment in adults with both chronic and episodic migraine (CM and EM) and

documented inadequate response to 2-4 classes of migraine preventive medications. Efficacy in a subgroup of patients with medication overuse (use of any acute medication on ≥15 days/month or triptans/ergots/combination medications on ≥10 days/month) at baseline was evaluated.

Methods: Patients were randomized (1:1:1) to quarterly fremanezumab (Month 1: 675mg; Month 2 and 3: placebo), monthly fremanezumab (Month 1: CM, 675mg; EM, 225mg; Month 2 and 3: 225mg), or matched monthly placebo for 12 weeks. Changes from baseline in monthly migraine days and headache days of at least moderate severity at 4 weeks and during 12 weeks of treatment were compared using a mixed-effect model for repeated measures.

Results: Of 838 randomized patients, 427 had medication overuse. Treatment with quarterly and monthly fremanezumab versus placebo resulted in significantly greater reductions from baseline in the monthly average number of migraine days at 4 weeks (least-squares mean [SE] change from baseline, −3.7 [0.62] and −4.5 [0.57] vs −0.0 [0.62]; $P<0.0001$) and over 12 weeks (−3.3 [0.62] and −4.5 [0.57] vs −0.5 (0.62); $P<0.0001$). With quarterly and monthly fremanezumab versus placebo, significant reductions from baseline were also observed in the monthly average number of headache days of at least moderate severity at 4 weeks (−4.3 [0.62] and −5.1 [0.56] vs −0.2 [0.62]; $P<0.0001$) and over 12 weeks (−4.0 [0.62] and −5.0 [0.56] vs −0.8 [0.62]; $P<0.0001$).

Conclusions: Quarterly and monthly fremanezumab provided early and sustained reductions in migraine and headache days vs placebo in patients with medication overuse and documented inadequate response to 2-4 classes of migraine preventive medications.

231. Efficacy and Safety of Fremanezumab in Patients with Episodic and Chronic Migraine and Documented Inadequate Response to 2-4 Classes of Migraine Preventive Medications during the Open Label Period of the Phase 3b FOCUS Study

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Introduction: Fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), has demonstrated efficacy and favorable safety and tolerability as a preventive treatment for migraine in adults with episodic or chronic migraine (EM or CM) who previously had an inadequate response to 2-4 classes of migraine preventive medications in the 12-week, double-blind FOCUS study. The efficacy and tolerability of fremanezumab in the 12-week open-label extension (OLE) of the phase 3b FOCUS study were evaluated.

Methods: The FOCUS study included a 12-week, double-blind, placebo-controlled treatment period (DBP) and 12-week, open-label treatment period (OLE). Patients were initially randomized (1:1:1) to quarterly fremanezumab (Month 1/2/3: 675mg/placebo/placebo), monthly fremanezumab (Month 1/2/3: 675mg[CM],225mg[EM]/225mg/225mg), or matched monthly placebo for the 12-week DBP. All patients completing the DBP entered the OLE and received three monthly doses of fremanezumab (225mg). Changes from baseline (assessed during 28-day run-in period before first double-blind dose) in the monthly average number of migraine days (primary endpoint) and headache days of at least moderate severity over the 12 weeks of the OLE were evaluated and summarized by double-blind randomization group.

Results: Of 838 patients randomized, 807 completed the DBP and entered OLE. All 807 patients completed the OLE. In the placebo, quarterly fremanezumab, and monthly fremanezumab groups, respectively, mean (standard deviation [SD]) changes from baseline in the monthly average number of migraine days over the 12 weeks of the OLE were −4.7 (5.41), −5.1 (4.71), and −5.5 (4.96). Mean (SD) changes in monthly average headache days of at least moderate severity were −4.5 (5.04), −4.8 (4.47), and −5.2 (4.94), respectively. The most common adverse events (AEs) during the 12-week OLE were injection-site reactions, such as injection-site erythema (6%), and there were low rates of AEs leading to discontinuation (<1%) and serious AEs (3%).

Conclusions: Fremanezumab demonstrated sustained efficacy, over 6 months in the double-blind fremanezumab treatment groups, and was well-tolerated long-term in patients with EM or CM and inadequate response to multiple migraine preventive medication classes.

232. Safety and Tolerability of Fremanezumab in Patients with Episodic and Chronic Migraine: A Pooled Analysis of Phase 3 Studies

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Introduction: The safety and tolerability of fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), has been evaluated in three randomized, double-blind, placebo-controlled phase 3 trials. This pooled analysis evaluated the safety and tolerability of fremanezumab in patients with episodic migraine (EM) and chronic migraine (CM).

Methods: This analysis of fremanezumab safety and tolerability included data from the 2 HALO studies (one in EM and one in CM) and the FOCUS study in patients with EM or CM and prior inadequate response to 2-4 classes of preventive medications. In all 3 trials, patients were randomized 1:1:1 to receive subcutaneous injections of fremanezumab quarterly (Months 1/2/3: EM or CM, 675mg/placebo/placebo), fremanezumab monthly (Months 1/2/3: EM, 225mg/225mg/225mg; CM, 675mg/225mg/225mg) or placebo monthly over 12 weeks. Adverse events (AEs), serious

AEs (SAEs), and AEs leading to discontinuation were summarized descriptively.

Results: Across the three phase 3 studies, 1,897 patients received fremanezumab (quarterly fremanezumab [675mg], n=943; monthly fremanezumab [225mg/225mg/225mg], n=401; monthly fremanezumab [675mg/225mg/225mg], n=553) and 945 received placebo. AEs were reported for similar proportions of patients across treatment groups (quarterly fremanezumab, 65%; monthly fremanezumab [225mg/225mg/225mg], 59%; monthly fremanezumab [675mg/225mg/225mg], 64%; placebo, 58%). With quarterly fremanezumab, monthly fremanezumab (225mg/225mg/225mg), monthly fremanezumab (675mg/225mg/225mg), and placebo, AEs leading to discontinuation (1%, 1%, 2%, and 2%, respectively) and SAEs (<1%, <1%, 1%, and 2%, respectively) were infrequent across treatment groups. In the quarterly fremanezumab, monthly fremanezumab (225mg/225mg/225mg), monthly fremanezumab (675 mg225mg/225mg), and placebo groups, respectively, the most common AEs were injection-site pain (22%, 22%, 19%, and 20%), injection-site induration (15%, 19%, 18%, and 13%), and injection-site erythema (16%, 14%, 16%, and 12%).

Conclusions: Over 12 weeks, fremanezumab was well tolerated in >1,800 patients with migraine, even in those with difficult-to-treat migraine. Discontinuations due to AEs and SAEs occurred in ≤1% of patients treated with fremanezumab.

233. Pooled Analysis of Cardiovascular Safety with Fremanezumab Treatment in Patients with Migraine by Cardiovascular History and Number of Cardiovascular or Cerebrovascular Risk Factors

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Introduction: Fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), has proven efficacy for the preventive treatment of migraine in adults. Given the vasodilatory properties of CGRP, the cardiovascular (CV) safety of fremanezumab in patients with migraine was evaluated in subgroups with and without a CV medical history and in subgroups with cardiovascular/cerebrovascular risk factors (CVRFs) at baseline.

Methods: This pooled analysis included data from three phase 3 trials (HALO EM, HALO CM, and FOCUS), in which patients with episodic migraine (EM; HALO EM) or chronic migraine (CM; HALO CM) and prior inadequate response to 2-4 classes of preventive medications (FOCUS) were randomized 1:1:1 to receive subcutaneous quarterly fremanezumab (Months 1/2/3: EM or CM, 675mg/placebo/placebo), monthly fremanezumab (Months 1/2/3: EM, 225mg/225mg/225mg; CM, 675mg/225mg/225mg) or matched monthly placebo over 12 weeks. CV adverse events (CV AEs) were evaluated by CV medical history, and cardiac and vascular disorder AEs (CVAEs) were evaluated by number of CVRFs at baseline.

Results: Of 2,842 pooled patients, 478 had a CV medical history (quarterly fremanezumab, n=167; monthly fremanezumab, n=158; placebo, n=153). Cardiovascular AEs occurred in similar, low proportions of patients across treatment groups (quarterly fremanezumab, 4%; monthly fremanezumab, 6%; placebo, 3%). Among patients without CV medical history (quarterly fremanezumab, n=776; monthly fremanezumab, n=796; placebo, n=792), CV AEs also occurred in similar, low proportions of patients across treatment groups (2%, 2%, and 2%, respectively). Additionally, 499 of the 2,842 total pooled patients had ≥2 CVRFs. CV risk factors included hypertension, smoking, obesity, diabetes mellitus, hypocysteinemia, atrial fibrillation, impaired glucose tolerance, lipid metabolism disorders, sleep apnea, tachycardia, albuminuria, a history of CV disease, abnormal ECG, and use of hormonal birth control pills. Over 12 weeks of double-blind treatment, cardiac disorder AEs were infrequent in patients with ≥2 CVRFs (placebo, 3%; quarterly fremanezumab, <1%; monthly fremanezumab, <1%) or ≥3 CVRFs (2%, 0%, and 2%, respectively), as were vascular disorder AEs (≥2 CVRFs, 2%, 3%, and <1%, respectively; ≥3 CVRFs, 3%, 4%, and 2%, respectively); no CVAEs were reported in patients with ≥4 CVRFs. No CV safety signals were identified.

Conclusion: This pooled analysis demonstrates that fremanezumab was well tolerated in migraine patients regardless of CV medical history and CVRFs, further supporting the favorable safety profile of this anti-CGRP preventive treatment.

234. Efficacy with Fremanezumab in Migraine Patients with Comorbid Moderate to Severe Depression and Documented Inadequate Response to 2-4 Classes of Migraine Preventive Treatments: Subgroup Analysis of the Randomized, Placebo-Controlled FOCUS Study

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Introduction: The FOCUS study of fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets the calcitonin gene-related peptide (CGRP), was the first and largest study of a migraine preventive treatment in adults with both chronic and episodic migraine (CM and EM) and documented inadequate response to 2-4 classes of migraine preventive medications. A post hoc subgroup analysis evaluated efficacy in patients with comorbid moderate to severe depression (Patient Health Questionnaire-9 score ≥10).

Methods: Patients were randomized (1:1:1) to quarterly fremanezumab (Month 1: 675mg; Month 2 and 3: placebo),

monthly fremanezumab (Month 1: CM, 675mg; EM, 225mg; Month 2 and 3: 225mg), or matched monthly placebo for 12 weeks. Changes from baseline in monthly average migraine and headache days of at least moderate severity were evaluated in patients with moderate to severe depression. Patients with significant psychiatric issues (eg, major depression) that, in the investigator's opinion, would compromise the patient's ability to participate in the study were excluded.

Results: Of 838 randomized patients, 154 had moderate to severe depression and were included in these analyses. Reductions from baseline in monthly average migraine days were significantly greater with fremanezumab vs placebo at 4 weeks (least-squares mean [standard error] change: quarterly, −3.5[0.91]; monthly, −3.5[0.95] vs 0.9[1.03]; $P<0.001$) and 12 weeks (quarterly, −3.2[0.93]; monthly, −3.9[0.97] vs 0.2[1.05]; $P<0.01$). Reductions from baseline in monthly average headache days were significantly greater with fremanezumab vs placebo at 4 weeks (quarterly, −4.5 [1.01]; monthly, −4.5[1.07] vs −0.1[1.16]; $P\leq0.001$) and 12 weeks (quarterly, −4.3[1.01]; monthly, −4.7[1.06] vs −0.8[1.15]; $P<0.01$).

Conclusions: Fremanezumab demonstrated efficacy, based on reductions in monthly migraine and headache days, vs placebo in patients with migraine, moderate to severe depression, and inadequate response to 2-4 classes of migraine preventive medications.

235. Pneumocephalus: A Unique Complication of Mastoiditis and Cerebral Venous Sinus Thrombosis

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Case Report: A 19 y/o AAF who was 16 weeks pregnant (G2P1) was treated with oral antibiotics and pain medications by her obstetrcian and primary care physicians for chronic otitis media, which she had since childhood. She presented to our ER with dizziness, fever and chills, nausea and vomiting, and severe right frontal headache. Vital signs were Temp 38.5 C°, HR 144 bpm, BP 110/83, RR 44. Examination was unremarkable except for right ear drainage. Computerized brain venography revealed right mastoiditis with bony erosion and cerebral venous sinus thrombosis that involved the right jugular vein and extended intracranially into the sigmoid and transverse sinus. The thrombosed sinuses contained multiple air pockets. Magnetic resonance venogram confirmed absence of flow in the right transverse and sigmoid sinuses. Blood cultures grew *Peptoniphilus indolicus* and *Bacteroides fragilis,* both notorious gas-producing anaerobic bacteria. Emergent surgical debridement and broad spectrum intravenous antibiotics resolved the patient's symptoms.

Discussion: Transverse or lateral sinus thrombosis secondary to otitis media is an uncommon complication in children and rarer in adults. This case of chronic otitis media in a pregnant adolescent evolved to mastoiditis and septic cerebral venous sinus thrombosis. Air pockets in the venous sinuses may have been due to bone erosion of the mastoid air cells or *in situ* gas formation by anaerobic Bacteroides or Peptoniphilus bacteria.

236. Alien Limb Can Be a Headache: A Rare Migraine Presentation

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Introduction: Alien limb syndrome is a phenomenon with involuntary, yet goal-directed movement. It is associated with structural lesions such as tumors, aneurysms, and strokes that affect corpus callosum, posterior parietal cortex, supplementary motor area and, anterior cingulate cortex. Herein, we report a rare case of alien limb syndrome that presented as a migraine aura.

Case: A 71-year-old man with a history of migraine headaches with an ocular variant, who presented with left hemiplegia and hemisensory loss. The patient suddenly developed left arm and leg weakness lasting for 15 minutes that was followed by tingling sensation over his left face and arm. By the time he arrived at the emergency department, his weakness improved however his left arm was trying to raise up and he had to keep it down using his other arm. For the next few hours, he continued to experience intermittent involuntary left arm elevation, and, in many instances, his left arm was trying to scratch his head, and eventually, he had 5/10 holo-cranial headache, nausea and vertigo. During the entire event, he remained hemodynamically stable with normal blood indices, comprehensive metabolic panel, and negative urine drug screen. All imaging studies were unremarkable including CT head, MRI brain, and CT angiogram head. He was treated with intravenous magnesium sulfate, prochlorperazine, and normal saline bolus hydration, and his symptoms resolved and was discharged home.

Conclusions: Migraine with aura should be considered in the differential diagnosis for alien limb syndrome especially if transient with normal workup.

237. Self-Reported Ace Exposure in Adolescents Increases Odds of Frequent Headache: A Cross-Sectional Analysis

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Objective: The association between exposure to adverse childhood experiences (ACEs) and increased headache has been well characterized in adults. Childhood adversity and its effect on headache has not been investigated as robustly in children. This study examines the relationship of ACEs to frequent headache in a cohort of adolescents.

Methods: The National Longitudinal Study of Adolescent to Adult (Add) Health followed a nationally representative sample of adolescents from 1994 to 2018 assessing health and social issues. We used publicly available data from Wave I of Add Health (N=6,504) to examine a variety of ACE exposures and their potential relationship to frequent headache. Logistic regression was used analyze the relationship between

cumulative ACE score and frequent headache while controlling for age, sex, race, food insecurity, and housing insecurity.

Results: The study population was comprised of 6,504 participants; 3,147 men (48.4%) and 3,356 women (51.6%). The mean age of respondents was 16-years-old. Sixty-six percent of participants were white. Frequent headache was reported in 29.3% of respondents (21% of males and 37% of females). Forty-five percent of respondents reported one or more ACE exposures. The most commonly reported ACEs were paternal alcoholism (12%) and 2 ACEs under community violence, witnessing (12.1%) or experiencing (12.5%) a shooting or stabbing. The ACEs that showed the strongest association with headache frequency were lack of maternal warmth, lack of paternal warmth, suicide attempt of family member, experiencing community violence, and living in an unsafe neighborhood (Table 3). After adjusting for demographic factors (sex, race, and food and housing insecurity-which together served as proxies for low income status), statistically significant adjusted odds ratios of frequent headaches ranged from 1.23 (CI 1.01, 1.50 p = .039) for not feeling safe in neighborhood to 2.34 (CI 1.43-3.83, p = .001) for personally experiencing a shooting or stabbing. For each increase in cumulative ACE score, odds of frequent headache increased by 1.2 (odds ratio 1.2, 95% confidence interval 1.15-1.3).

Conclusions: A variety of ACE exposures was associated with frequent headache in adolescents. An increase in cumulative ACE exposure increased odds of having frequent headache. Further investigation should be performed in children to both clarify the relationship between childhood adversity and headache and to inform our understanding of pathophysiology and potential treatments.

238. # Headache: When a Common Problem Becomes a Neurological Emergency in Acute Stroke Patients

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Background: Headache is frequently reported in acute stroke patients, yet remains poorly understood. The International Classification of Headache Disorders Third Edition lists over 50 types of headaches and the most fundamental classification is to distinguish between primary and secondary headache. The challenge of making this distinction when managing acute stroke patients, is, at its core, determining when a headache problem is a neurological emergency; most notably, when headache pain is a manifestation of a neurological change signifying another acute ischemic event or an acute hemorrhage. Thus, the purpose of this project was to assess the knowledge of current neurology residents regarding the problem, and to develop an algorithm to assist neurology residents in the evaluation and management of headache in the acute stroke patient.

Methods: We conducted a survey of neurology residents at the University of Kentucky, to evaluate the level of understanding of primary and secondary headaches, to assess current practices, and to determine whether a structured protocol would aid in the management of these patients.

Results: Greater than 93% of neurology residents (14 of 15 respondents) surveyed at the University of Kentucky reported having a clear or fairly clear understanding of the difference between primary and secondary headache, and 80% reported understanding the mechanisms that drive headache pain in stroke patients. However, only 60% have a process to further characterize headache in acute stroke patients. Only 46.7% (n=7) reported "always" going to bedside to evaluate new headache in the stroke patient, and 33.3% (n=5) felt that this problem could be handled by phone. More than 90% reported "always" or "often" avoiding sedating medications that might impact subsequent neurological assessments.

Conclusion: While the majority of neurology residents seem to have adequate knowledge regarding the difference between primary and secondary headache disorders, there appears to be a practice gap in the need for a bedside evaluation process to determine possible neurological deterioration. Based on these data, an algorithm could be helpful in distinguishing between headache that may be a harbinger of neurological complication and those that are secondary to the acute stroke itself. Further, while the majority of residents would appropriately avoid sedating medications, a consensus regarding medical management has not been established. A future aim of this project is to develop an algorithm for evaluation and a protocol for treatment of acute stoke-related headache.

239. A Unique Case of Metal Allergy in an Occipital Nerve Stimulator Implant

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Background: This case describes a rare allergic reaction with the metal from an occipital nerve stimulator implant and iodized salt. To our knowledge, this is the first such case described in the literature.

Case Description: A 58-year-old male with history of hypertension, coronary artery disease, pituitary adenoma s/p radiation therapy, adrenal hypofunction, iodine contrast allergy, and chronic occipital neuralgia. This patient presented to the clinic for occipital nerve stimulator trial after multiple failed attempts at conservative therapy including physical therapy, medications, and injections. After successful trial, the patient underwent an occipital nerve stimulator implant. Two months after successful implantation, his occipital neuralgia symptoms subsided. However, he started to notice that when he consumed iodized salt, he would break out in an erythematous rash over the implant site, trunk, and extremities. Allergy testing confirmed allergy to metal ingredients within the implant hardware. The patient was then successfully treated with a daily regimen of cetirizine.

Conclusion: This is the first report of an allergic reaction involving a metal implant and ingestion of iodized salt. Additional research is required to develop protocols and define management of allergy to implantable stimulators.

Health Services Research

101. Multi-Objective Predictive Control of Covid-19 Epidemics and Mental Health

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Introduction: As the COVID-19 pandemic wears on, it is likely the mental health burden will increase as measures taken to slow the spread of the virus, such as social distancing, business and school closures, and shelter-in-place orders, lead to greater isolation and potential financial distress. Hence a control strategy that balances social measures with mental health in necessary. We model the pandemic as extended Susceptible Exposed Infected Recovered (SEIR) dynamics and optimally control the embedded social interaction parameter ensuring the number of patients stay under hospital threshold with minimal social restrictions thereby limiting mental stress.

Methods: The goal of infectious-disease intervention is to keep COVID-19 patients under hospital capacity, while not causing unnecessary social distancing leading thereby limiting poor mental health outcomes such as depression, anxiety, distress and substance use. First, the extended SEIR model parameters such as incubation, recovery, mortality rates are tuned to match the actual pandemic data from WHO. Next, a predictive controller (computes the optimal sequence in time of social interaction parameter values to be imposed on the system to control the number of COVID-19 patients just below the hospital capacity. To compute this sequence, the controller uses the extended SEIR model for prediction and optimizes a multi-objective cost function that minimizes both COVID-19 patients and mental illnesses by checking a multitude of different social restriction sequences. The actual government policies can then be decoded from the level of social interaction parameter. After each week, new data on the virus spread is used to recalibrate the model, and the controller recomputes and implements a new optimal sequence of social measures.

Results: A multi-level intervention control sequence that corresponds to quarantine screening and isolation, business closures, cancellation of events and business as usual, is considered. The results from the predictive controller are encouraging as the number of patients stay strictly below hospital limits and exhibit minimal oscillations. Importantly, the controlled social interventions are minimal thereby limiting associated mental illnesses such as stress, anxiety, depression and substance use.

Conclusion: The predictive controller computed a sequence of optimal social interaction measures, by optimizing a multi-objective cost function ensuring the hospital occupancy of COVID-19 patients is met with minimal social and economic restrictions thereby limiting anxiety and mental stress. [1] Alleman, T et.al. *Covid-19: from model prediction to model predictive control*. Ghent University, 2020.

102. Population-Based Incidence Estimate of Anti-NMDA Receptor Encephalitis in New York City

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Background: Anti-NMDARE is one of the most common and well-described forms of autoimmune encephalitis, however, few studies have assessed its overall incidence. This study aims to derive a population-based estimate of anti-NMDA receptor encephalitis (anti-NMDARE) incidence in New York City.

Design/Methods: Cases were identified from The Rare Epilepsy of New York City (RENYC) database, which includes medical records for all patients with a visit associated with ICD-9 code 345.x (epilepsy), 779.0 (neonatal convulsions), or 780.39 (convulsions) from five academic medical centers in Manhattan and the Bronx between 2010-2014. This database was queried for the search term "NMDA," and identified cases were reviewed to confirm that consensus criteria were met for definite diagnosis of anti-NMDARE. Those who lived in either Manhattan or the Bronx and who received their initial care within the study period were included in analyses. For incidence calculations, borough populations for each study year were obtained from city census data. It was anticipated that this search strategy may have resulted in the following potentially missed cases: those who did not have seizures (per prior literature, range 23-32%) and those who may never have received care at a study site hospital (per assessment of all hospital bed sizes in each borough, up to 22%).

Results: 38 individuals with anti-NMDARE were identified, of whom 15 met inclusion criteria. Nine included individuals (60%) resided in Manhattan and six (40%) in the Bronx. Median age at symptom onset was 21 years (range 2-41 years), and 12 included individuals (80%) were female. Eight included individuals (53%) received care at more than one hospital, of whom three (20%) received care at multiple study site hospitals. The median time from symptom onset to hospital presentation was 6.5 days (range 0 to 84 days), and the median time from hospital presentation to treatment initiation was 21 days (range 0 to 378 days). An incidence estimate of 0.10/100,000 (confidence interval: 0.06-0.17) new cases per year was derived based on identified cases. Accounting for potentially missing cases yielded an overall incidence estimate of up to 0.18/100,000 (confidence interval: 0.11-0.25) new cases per year.

Conclusion: This study provides a population-based estimate of anti-NMDARE incidence in New York City.

Understanding the demographic and clinical characteristics of individuals with anti-NMDARE in this large, diverse city will enable the future design of diagnostic/management tools and interventional studies.

103. Increasing Out-of-Pocket Costs for Privately-Insured Neurology Patients

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Objective: Out-of-pocket costs have increased recently for patients as health insurers and employers attempt to contain spending and high deductible health plans proliferate. These costs influence healthcare utilization, yet out-of-pocket costs for neurologist care have not been characterized. In this study, we aimed to measure out-of-pocket costs of evaluation and management (E/M) services and common diagnostic testing for neurology patients.

Methods: Using healthcare claims data for individuals insured by UnitedHealthcare from January 2001 to June 2016, we identified patients with a neurologist visit or a diagnostic test ordered by a neurologist. We assessed inflation-adjusted out-of-pocket costs for E/M visits, neuroimaging (magnetic resonance imaging- MRI, computed tomography-CT, and carotid ultrasound- CUS), and neurophysiologic testing (electromyogram/nerve conduction studies- EMG/NCS, electroencephalogram- EEG, and polysomnogram-PSG). Outcomes included the proportion of patients with out-of-pocket costs for a specific diagnostic service each year and the 50th and 95th percentile of out-of-pocket cost for patients with any out-of-pocket cost.

Results: In total, 3,724,342 patients with a neurologist visit or test ordered by a neurologist were identified. The proportion of patients that paid out-of-pocket costs in any given year for E/M visits ranged from 86.5% to 95.2%. The proportion of patients that paid out-of-pocket costs in any given year for diagnostic tests ranged from 23.1% to 69.5% and increased throughout the study period. For patients paying any out-of-pocket costs, the median amount increased from 2001 to 2016: E/M ($15 to $40; 167% increase), MRI ($48 to $103; 116% increase), CT ($25 to $46; 83% increase), CUS ($20 to $38; 92% increase), EMG/NCS ($20 to $75; 274% increase), EEG ($20 to $71; 255% increase), and PSG ($29 to $86; 199% increase). Out-of-pocket costs varied considerably across patients and a small number of patients paid a large amount. In 2016, patients in the 95th percentile of out-of-pocket costs paid $147 per E/M visit, $875 for MRI, $331 for CT, $193 for CUS, $538 for EMG/NCS, $375 for EEG, and $561 for PSG.

Interpretation: The proportion of privately-insured patients that pay out-of-pocket for neurologic diagnostic services is increasing and out-of-pocket costs are on the rise. The out-of-pocket cost per test varies greatly across patients and is substantial for some patients. As such, neurologic evaluation might lead to financial hardship for patients and/or lead to decreased healthcare utilization with unknown impact on clinical outcomes.

104. Patient Travel for Neurologist Visits and Implications for Telemedicine: A US Population-Based Medicare Study

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Objective: The regional density of neurologists in the US varies by 4-fold. We aimed to measure the proportion of patients who travel for neurologist visits, neurologic conditions that account for out-of-region visits, and predictors of travel.

Methods: We identified outpatient neurologist evaluation and management (E/M) visits from a 2015 20% Medicare sample. Travel for care was defined as having a neurologist E/M visit outside of the patient's Hospital Referral Region (HRR). Distance traveled was calculated as miles between patient and neurologist zip codes. Multivariate logistic regression was used to determine the association of patient (demographics, neurologic conditions) and regional characteristics (neurologist density quintiles) with travel.

Results: We identified 513,776 Medicare beneficiaries with a neurologist E/M visit. Of these, 105,687 (20.6%) traveled for care. Average distance was 148.7 miles (95%CI: 147.1-150.2) for patients who traveled compared to 12.4 miles (95%CI: 12.4-12.5) for patients who did not. The most common neurologic conditions among patients who traveled for care were dementia (13.2% [13,983/105,687]), peripheral neuropathy (12.8% [13,561/105,687]), and epilepsy (12.8% [13,531/105,687]). Across conditions, the proportion of patients who traveled for care ranged from 17.8% (5789 out of 32,495) of patients with sleep disorders to 26.0% (5134 out of 19,755) of patients with multiple sclerosis. Patients who resided in the lowest neurologist density regions had the highest proportion of travel for care across all neurologic conditions (overall 1st quintile [low]:34.9%, 2nd quintile:24.0%, 3rd quintile:22.3%, 4th quintile:16.6%, 5th quintile [high]:18.3%). Factors associated with travel for care were low neurologist density (1st quintile:OR 2.28[95%CI: 2.23-2.33], 2nd quintile:OR 1.38 [95%CI: 1.35-1.41], 3rd quintile:OR 1.25 [95%CI: 1.23-1.27] compared with the highest quintile), white race (OR 1.13 [95%CI:1.10-1.16] compared with black), younger age (OR 0.989 [95%CI: 0.988-0.989]), not dual-eligible (OR 1.17 [95%CI: 1.15-1.19]), male (OR 1.04 [95%CI: 1.02-1.05]), and no primary care (OR 1.82 [95%CI: 1.79-1.86]) or non-neurologist specialist (OR 1.97 [95%CI: 1.91-2.03]) visit within the home region for their neurologic condition.

Conclusions: We found that about 1 in 5 individuals who see a neurologist traveled out-of-region to the visit and the average travel distance was ~150 miles. The largest predictor of travel was low neurologist density in the home region.

These data provide insight for policymakers regarding the potential of telemedicine to provide more accessible neurologist care. Future studies could evaluate outcome differences for people who travel out-of-region compared with those who do not.

105. Neurological Comorbidities in Hospitalized Patients with Opioid Abuse

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Objective: Determine the prevalence, nature, and the burden of neurological comorbidities in hospitalized patients with opioid abuse.

Background: Although ravages born of the nationwide opioid epidemic crisis are well chronicled, little is known about neurological comorbidities associated with opioid abuse.

Design/Methods: We analyzed University of Kentucky Healthcare Enterprise discharge data for 34,414 subjects during October 1, 2016-September 30, 2017. Patients with opioid abuse were identified by using ICD-10: F11. - Mental and behavioral disorders due to use of opioids. Of 2,183 opioid abuse subjects identified, 360 were selected for chart review matched for age, gender, race, and urban-rural residence. Four neurologists reviewed the medical records; 90 records were randomly assigned to each investigator and no statistically significant inter-rater disagreement identified. Thirteen subjects had no documentation of opioid abuse, leaving 347 subjects for analysis.

Results: Among discharged patients, opioid abuse prevalence was 6.3% and significantly more prevalent among younger patients (Mean: 40; SD: 12.8; $p<0.0001$), women (55.4%; $p<0.0001$), Caucasians (95.3%; $p<0.0001$), and urban population (29.1%; p 0.0277). Of 347 subjects with opioids abuse reviewed, 179 (51.6%) had any neurological comorbidities. The latter, frequently overlapping, included encephalopathy causes (130; 72.63%), neuromuscular disorders (42; 23.46%), seizure disorders (23; 12.85%), spine disorders (23; 12.85%), strokes (20; 11.17%), central nervous system (CNS) infections (3; 1.67%), and movement disorders (2; 1.12%). No posterior reversible encephalopathy syndrome (PRES), leukoencephalopathy, or transverse myelitis identified. Neurological comorbidity contributed to the admission decision in 162 subjects (46.69%).

Conclusions: Neurological comorbidities are a frequent and heretofore underappreciated contributor to the disease burden of those with opioid abuse. Comorbidities traditionally ascribed to opioid abuse were not found in this study. The importance of neurological comorbidities should be considered in the public health discussions surrounding opioid epidemic crisis.

106. Does Socioeconomic Status Predict Fetal Brain Volumes?

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Background: Socioeconomic status (SES) predicts neurodevelopmental outcome in both healthy infants and preterm infants at risk for neurodevelopmental sequelae. Recent data report associations between SES and structural brain volumes and connectivity in early childhood. It is not yet known whether these brain differences emerge *in utero* or are shaped by environmental factors after birth. We sought to determine whether structural brain associations with SES can be detected *in utero*, and whether this association differs between healthy fetuses and those with a neurodevelopmental risk, specifically congenital heart disease (CHD). We hypothesized that higher levels of maternal education would predict larger cortical and proliferative compartment volumes, while lower income levels would be associated with smaller limbic volumes related to greater maternal stress. We expected associations to be more robust among the at-risk CHD group than the controls.

Methods: From 2014-2018, we recruited pregnant women with healthy fetuses and those with CHD-affected fetuses for a longitudinal, prospective cohort study of fetal brain development in CHD. We obtained structural fetal brain MRI at two timepoints between 18-40 weeks gestation. We generated a super-resolution reconstruction and applied a semi-automated spatiotemporal fetal brain MRI atlas to measure total and regional brain volumes. Education and income level characterized SES through self-report questionnaires. We applied linear regression to assess the effects of education and income on total and regional brain volumes, adjusting for gestational age, fetal sex, and CHD status. We explored interactions between SES variables and CHD status.

Results: 177 fetuses, including 74 with CHD and 103 controls had data available for analysis. Higher income was associated with larger total brain volume (P=0.02), and with regional volumes of the fetal cortex (P=0.007), subcortical gray matter (P=0.03), and proliferative compartments (P=0.004). Education was not associated with total brain volume, though higher levels of education predicted larger subcortical gray matter (all P<0.02). There were no significant interactions between fetal CHD status and either SES measure.

Conclusion: These findings suggest that SES, and in particular income level, is associated with structural brain development even before birth. While further studies are needed to determine causal inference, it is possible that environmental factors associated with lower income such as stress, toxin exposures, or other maternal health factors may influence fetal brain structure potentially with lasting consequences for child neurodevelopment.

107. Social Factors Related to Home-Based Telerehabilitation after Stroke

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Objective: We designed a 12-week telerehabilitation (TR) program for stroke patients and evaluated which social factors might be important to achieve motor gains and improved mood.

Background: Telemedicine is now, in the context of COVID-19, more clinically relevant than ever as a major source of outpatient care. Stroke patients require high doses of activity-based rehabilitation yet often face barriers in cost, compliance, and access. Home-based TR may be useful for addressing these issues. Social support influences stroke outcomes, and social networks can affect engagement in therapy programs.

Methods: Adult stroke patients (n=13) with arm motor deficits saw a licensed OT/PT who performed a live exam followed by supervised home-based TR (12 weeks, 6 days/week, 1 hour/day). At the 6-week midpoint, each patient's social network was mapped, producing measures of network size, density and constraint. With these measures, we tested the following hypotheses: first, social network measures are associated with the MOS-SSS, an established measure of social support. Second, social network measures are positively related to (1) arm motor gains (change in score on the 66-point arm motor Fugl-Meyer scale (FM)), (2) walk time improvement (10m walk test), and (3) improved mood (change in Geriatric Depression Score (GDS)). Finally, we compared social networks of TR patients with a cohort of 176 stroke patients with social network data who did not receive any TR to identify structural differences in support.

Results: Over 12 weeks, median FM score significantly improved from a baseline of 46 [42-57] to 59 [52.5-61.5] (p=0.002). Social network size was related to social support (r=0.69, p=0.018) and improved mood (r=0.679, p=0.015). Network density was related to arm motor gains (r=0.75, p=0.003). Both size and density were related to walk time improvement (r=0.61, p=0.025; r=0.80, p=0.003, respectively). TR patient networks were larger (p=0.012) and less dense (p=0.046) than control networks.

Conclusions: High doses of home-based TR for 12 weeks is feasible and improves motor outcomes. In this pilot study with limited sample size, social network size was validated against MOS-SSS. Size was related to walk time and improved mood, and network density was related to arm motor and walk time gains in response to intensive TR. Finally, TR patients had larger and more open social networks than stroke patients who did not receive TR. Understanding how social networks intersect with TR outcomes is crucial as we transition towards virtual models of care.

108. Twelve-Year Rates and Causes of Admissions among Those with Neurological Conditions in the US: A Nationally Representative Study

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Objective: We examined rates and causes of hospital admission among patients with the following neurological conditions: Brain Tumors (BT), Motor Neuron Disease (MND), Multiple Sclerosis (MS), Parkinson's disease (PD), Spinal Cord Injury (SCI), Traumatic Brain Injury (TBI), Stroke, Cerebral Palsy (CP).

Background: Understanding hospital admissions rates and causes is key to allocating healthcare resources and implementing interventions to avoid preventable hospitalizations. To our knowledge, there are no comprehensive population-based investigations examining rates and causes of admissions among neurological patients in this timeframe.

Methods: We used the 2003-2014 National Inpatient Sample database, capturing a representative sample (20%) of US hospitalizations. Hospitalizations for the eight neurological conditions of interest (any diagnostic position) were identified using validated ICD-9-CM case definitions. Admission causes were identified using Clinical Classifications Software for Diagnosis Codes. Descriptive statistics were used to determine weighted rates of admission and top three causes of admissions.

Results: The admission rates in 2003 and 2014 were: BT (0.64%, 0.83%), MND (0.03%, 0.04%), MS (0.30%, 0.42%), PD (0.86%, 0.78%), SCI (0.13%, 0.18%), TBI (0.80%, 0.98%), Stroke (5.14%, 5.84%), CP (0.21%, 0.30%). For all conditions except PD and CP, the top cause of admission was consistent from 2003 to 2014. The top causes of admission for neurological conditions in 2003 and 2014 were: BT (secondary malignancies, 22.6%, 18.5%); MND (hereditary and degenerative nervous system conditions, 21.9%, 18.8%); MS (MS, 19.7%, 17%); SCI (SCI, 25.6%, 19.8%); TBI (intracranial injury, 57.7%, 57.6%); stroke (acute cerebrovascular disease, 28.5%, 29.1%). For PD, the top cause of admission changed from pneumonia (2003-2008) to septicemia (2009-2014). For CP, the top cause of admission changed from epilepsy/convulsions (2003-2012) to septicemia (2012-2014). Notably, from 2011-2014 septicemia was among the top three causes of all hospital admissions for all controls and neurological patients, except for BT and TBI.

Conclusion: Rates of admission remained largely consistent for all neurological conditions. All conditions except BT have at least one top cause of admission that is potentially preventable. Further emphasis on infection prevention in particular would likely reduce the occurrence of admission in those with neurological conditions.

109. Understanding and Informing Emergency Cardiovascular Disease Preparedness during the Coronavirus Outbreak among Vulnerable Populations

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Introduction: Acute stroke and acute myocardial infarction (AMI) treatments are available, and reduce disability and mortality, but are highly time-sensitive. In the setting of the COVID-19 pandemic, early data reveals a decrease in presentation and an increase in pre-hospital delay for acute stroke and AMI. Thus, we set out to understand the community's perception of seeking acute stroke and AMI care during the Coronavirus pandemic to inform future public health campaigns.

Methods: We developed an interview guide and a data collection form guided by the Theory of Planned Behavior (TPB). Interviews were recorded and conducted via phone to honor social distancing orders. Due to the time-critical information we were collecting, analysis of interviews was performed using a rapid assessment process (RAP) to streamline qualitative analysis. Data collection was conducted on structured collection forms, and subsequent data reduction of TPB domain themes were completed by two reviewers. Responses for AMI and stroke were compared.

Results: We conducted 15 semi-structured interviews from April 17 to May 7, 2020, reaching thematic saturation. The mean duration of interviews was 40.2 minutes. Participants were 73% female, mean age of 50.1, 80% African American, and 13.3% with high school education or equivalent. There was an unfavorable attitude towards going to the hospital due to uncertainty about coronavirus transmission at the hospital for both stroke and AMI, unclear hospital protocols, long wait time, and being sent home too soon. While participants felt it is riskier to stay at home than to go to the hospital in an acute emergent situation, there is an unfavorable attitude towards utilizing emergency medical services. They include uncertainty of COVID transmission from the ambulance, general fear of ambulances, cost, and time delay. Finally, participants reported they would be more cautious approaching strangers if they were to witness a stroke than prior to the pandemic.

Conclusions: The primary barriers to calling 911 and getting to the hospital as soon as symptoms start for stroke and AMI to be fear of viral transmission and concern for the hospital's capacity. Motivating factors included severe or worsening symptoms. There were no significant differences between responses to acute stroke versus AMI. If a Coronavirus resurgence should occur, we recommend unified public health messaging about the urgency of treatment and the promotion of the hospital's capacity to care for both COVID and non-COVID cases.

110. Monitoring Real-Time Data in a Randomized Clinical Trial through Web-Based Dashboards during Coronavirus Pandemic

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Background: Monitoring real-time enrollment and retention data during on an ongoing clinical trial may facilitate equitable enrollment and retention and may be particularly important during unanticipated current events, such as the Coronavirus pandemic. We describe the Reach Out web-based dashboard, a visual tracking system displaying participant recruitment and outcome trends, and its use in a stroke prevention trial during the Coronavirus Outbreak.

Method: Reach Out is a health system focused, multicomponent, health behavior theory based, mobile health behavioral intervention to reduce blood pressure among hypertensive patients evaluated in a safety-net emergency room in Flint, Michigan. The Reach Out dashboard is a web-based research tool that visually tracks trial measures of participant recruitment, retention and engagement. Trial process measures include participants that stop the intervention, responsiveness to self-reported blood pressure, and 6 or 12 month outcomes assessment completion. Our research team reviews the dashboard weekly and makes changes to trial strategies as needed.

Results: The dashboard has been in place since June 2019 and thus was in place during the State of Michigan stay at home order which was enacted on March 23rd of 2020. The dashboard facilitated changing to remote outcomes by allowing the research team to monitor: 1) changes in participant engagement with self-reporting blood pressure; 2) participants stops and withdrawals; and 3) completion rates of 6 and 12 month tele-outcomes.

Conclusion: The Reach Out clinical trial dashboard has aided in monitoring the impact of transitioning a stroke prevention trial to remote outcomes. We anticipate that it will also facilitate safely re-engaging in-person and continued remote outcomes among participants when stay at home orders are relaxed.

111. Adverse Childhood Experiences in Patients with Neurological Disease

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Objective: To describe the prevalence of adverse childhood experiences (ACEs) among neurology patients and determine the association between high ACEs, healthcare utilization rates, and comorbid mental health illness.

Background: ACEs have been linked to numerous medical conditions including cardiovascular disease, diabetes, and mental illness. An ACE score >4 has also been linked to increased healthcare utilization. There is limited knowledge about the prevalence of high ACEs in patients with neurologic diseases, its effect on healthcare utilization, and association with comorbid mental health illness.

Methods: This was a retrospective cross-sectional study of adult patients seen in follow up in an outpatient neurology practice at the Hospital of the University of Pennsylvania. We excluded new patients, patients with cognitive

impairment, incomplete questionnaires, and patients unable to respond to the questionnaire in English. Participants completed the ACE survey and depression and anxiety questionnaires (PHQ2 and GAD2) . Healthcare utilization was measured by number of patient-reported emergency department visits/hospitalizations and chart review of outpatient phone calls. Statistical associations were adjusted for age, gender, and race/ethnicity.

Results: There were 199 patients who met study criteria. 23.6% had high ACE scores. This proportion of elevated ACEs is higher in comparison to US population averages (23.9% vs 12.6%, p<0.01). High ACEs were seen across all neurological conditions, with the greatest percentage seen in Neuropathy (30%), Headache (29%), Stroke (28%), and Epilepsy (21%). Higher ACE scores were associated with increased ED utilization (OR=9.9, CI 1.7-11, p<0.01), increased hospitalizations (OR=3.5, CI 1.2-11, p<0.05), increased telephone encounter utilization (OR 2.9, CI 1.1-7.8, p=0.052), high PHQ2 depression scores (OR=8.2, CI 3.1-22, p<0.01), and high GAD2 anxiety scores (OR=4.1, CI 1.6-11, p<0.01).

Conclusion: Patients with neurological conditions are more likely to have high ACEs in comparison to the general population. These patients also have higher healthcare utilization, and a higher anxiety and depression scores. Addressing ACEs may be a potential mechanism to improve the management of patients with neurological conditions and decrease healthcare utilization.

112. Trends in Imaging Utilization and Hospitalization of Dizziness and Vertigo in US Emergency Departments (1995-2015)

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Background: Diagnosis of patients with dizziness and vertigo remains a challenge for healthcare providers in the emergency department (ED). An estimated ~$10 billion/year is spent on neuroimaging and hospital work-ups to detect the 3-5% with posterior fossa strokes. We sought to investigate long-term trends in imaging and hospital admissions among patients with dizziness/vertigo using a nationally representative sample of US ED visits.

Methods: We analyzed trends in national rates of imaging and hospitalization from 1995-2015. We used the Centers for Disease Control and Prevention's (CDC) National Hospital Ambulatory Medical Care Survey (NHAMCS), which analyzes a weighted sample of US hospital ED visits each year and provides an algorithm for systematic extrapolation to national estimates. We included patients ≥16 years old. The dizzy group included patients with vertigo/dizziness recorded as a reason-for-visit, a symptom diagnosis of dizziness recorded as a final diagnosis (ICD-9-CM 780.4), or any vestibular diagnosis recorded as a final diagnosis (ICD-9-CM 386.x). The control (non-dizzy) group included patients with reason-for-visit other than vertigo/dizziness and no final diagnosis of dizziness or vestibular disorder. We assessed trends in utilization of computed tomography (CT) scans, magnetic resonance imaging (MRI), and hospital admissions over time; we also compared these between the two study groups.

Results: From a sample of 623,765 records, the weighted estimate of patients included was 73.2 million with dizziness and 2.4 billion without. The dizzy group was 61% female and median age was 49 (IQR:30-68) For both groups there was a progressive upward trend in imaging utilization over time. Utilization of imaging (CT or MRI) in the dizziness population rose from 10.0% (95%CI: 6.7-13.4) in 1995 to 37.4% (95%CI: 32.2-41.6) in 2015. Utilization for the non-dizzy patients was just 3.4% (95%CI: 2.9-3.8) in 1995 and rose to 19.2% (95%CI: 17.8-20.7) in 2015. The mean ratio of CT to MRI was □15:1 in dizziness and □23:1 in non-dizzy patients. For both groups, annual hospital admissions remained relatively stable from 1995 to 2010—dizzy 18.2% (range 14.3-21.6), non-dizzy 14.9% (range 12.8-16.7)—after which (2011-2015) they declined substantially—dizzy 13.7% (range 11.4-16.1), non-dizzy 11.5% (range 9.2-13.9).

Conclusion: ED patients with dizziness are imaged and admitted more frequently than their non-dizzy counterparts. CT is grossly overused and MRI is underused. Admission rates have fallen, so there is an even higher premium on accurate bedside diagnosis of stroke in acute dizziness/vertigo.

113. Risk Factors for Diagnosis of Seizure in the Inpatient Stroke Code Population

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Background: An inpatient stroke code (ISC) is activated when an acute neurological event is suspected in a hospitalized patient. Although the primary purpose of an ISC is to rapidly respond to a potential stroke intervention case, anecdotal observation suggests that this pathway is activated for any acute neurological change. It is crucial to quickly differentiate between stroke, seizure and other diagnoses in order to allocate diagnostic and therapeutic resources properly.

Hypothesis: Within the ISC patient population, independent predictors of seizure can be identified.

Methods: An IRB approved, retrospective analysis of prospectively obtained data was performed for all ISCs between March 2017 and May 2018. Patients with diagnosis of seizure were identified based on chart review, diagnosis code, and EEG findings. These were compared to all others.

Variables of interest included demographics, comorbidities, and potential clinical risk factors. Wilcoxon Ranked Sum tests were used for continuous data and chi-square tests of proportion or Fisher's Exact test (for low expected frequencies) for categorical.

Results: Out of 211 inpatient stroke codes, 21 patients with diagnosis of seizure were identified as well as 75 patients with stroke and 115 with other diagnoses. Patients with seizure were younger, (median age 66 vs 72; p= 0.038); had a shorter time since last seen normal (15 vs 60 minutes (p=0.025) and were more likely to have reduced consciousness (85.7% vs 61.1%; p=0.026), unconsciousness (61.9% vs 11.6%; p <0.001), gaze deviation (28.6% vs 5.8%; p=0.003), aphasia (76.2% vs 43.7%, p=0.005), or motor weakness (81% vs 56.3%, p=0.03). None of the 21 patients with seizure had an acute stroke on imaging. Gender, diabetes, dialysis within 6 hours, sedative use, antiplatelet therapy, elevated level of care, neglect, dysarthria, sensory symptoms, ataxia, facial droop, dizziness, blood glucose abnormalities, and blood pressure did not significantly predict seizure.

Conclusions: A significant portion of ISC responses were for patients having a seizure or other acute event that was not a stroke. Patients with seizure were younger and had shorter time interval since last seen normal. Reduced level of consciousness, unconsciousness, gaze deviation, aphasia, and motor weakness each were significantly more likely to be seen in seizure than other diagnoses. This data will guide future improvement projects with goals of making rapid correct diagnosis, guide appropriate response and treatment, and ultimately improve outcomes of hospitalized patients with acute neurological event.

Interventional Neurology

309. Hypesthetic Ataxic Hemiparesis: Thinking Beyond the Conventional Paradigm

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Background: Ataxic hemiparesis (AH) is one of the traditional lacunar syndromes, and was first described by Fisher and Cole in 1965 as "homolateral ataxia and crural paresis."[1] It classically presents with ipsilateral weakness (leg>arm) and ataxia without sensory loss, and is due to damage to the corticospinal and the cerebellar pathways.

Objective: To describe a case of hemisensory loss in an otherwise classic case of ataxic hemiparesis.

Design/Methods: Retrospective chart review and literature search.

Report: A 60-year-old right-handed man with hypertension presented with sudden onset of right-sided arm and leg weakness along with gait instability. On examination, motor strength was 4/5 in the right upper and lower extremities; drift was noted in right upper extremity (RUE). Sensory examination was altered to light touch and temperature in the right upper and lower extremities with mild dysmetria on finger to nose in RUE on cerebellar examination. Magnetic resonance imaging of the brain showed an acute infarct involving the posterior left lentiform nucleus and adjacent corona radiata. Transthoracic echocardiogram did not reveal any source of cardioembolism.

Discussion: Typically, AH results from an infarct of ventral pons or posterior limb of the internal capsule, most commonly secondary to small-vessel disease[2]. Previous reports attributed the ipsilateral ataxia in AH to decreased blood flow in the cerebellar hemisphere contralateral to the site of the lesion, also known as crossed cerebellar diaschisis (CCD).[3] However CCD has been described in pure motor hemiparesis as well, so CCD does not solely explain the ipsilateral ataxia. More recently, the ataxia in AH is thought to specifically localize to the ipsilateral red nucleus dysfunction due to disruption of cortico-rubral pathway at the internal capsule.[3] In our patient, the corona radiata / lenticulocapsular infarct caused disruption of the corticospinal, cortico-rubral, and spinothalamic pathways leading to hemiparesis, hemiataxia and hemihypesthesia respectively.

Conclusion: Classic AH presents with ipsilateral weakness and limb ataxia without any known hypesthesia. Hypesthesia can be recognized as part of the clinical spectrum in AH and when present may indicate a more lenticulocapsular / corona radiata localization.

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310. Post-Lumbar Puncture Retroperitoneal Hematoma

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Introduction: Lumbar punctures are commonly performed procedures with several side effects that include, but are not limited to, headaches, back pain, and transient radiating lower extremity pain. Another less common complication is a post-lumbar puncture spinal hematoma, of which 75% occur in the epidural location (Al-Jishi, *Surgical Neurology International,* 2017). This case report discusses a rare massive retroperitoneal hematoma after a diagnostic lumbar puncture in a patient with normal coagulation and no other bleeding risk factors.

Case Report: A 75 year old male with prior history of dementia, stroke, and coronary artery presented with a new onset seizures. Studies underlying the etiology of the seizures were inconclusive, so a lumbar puncture (LP) was performed at bedside with a 6-inch, 20-gauge needle which resulted in an unsuccessful attempt at obtaining cerebrospinal fluid (CSF). After rehydrating the patient with intravenous fluids (IVF), a second LP was performed under fluoroscopy and obtained 14 cc of colorless CSF. The patient had a drop in hemoglobin from 12.5 prior to the second LP to 10.7 g/dL after the first LP and a continuous drop to 9.2 the next day. His coagulation panel showed normal INR at 1.1 and normal platelet count, and physical examination found a large ecchymosis on the right flank. Abdominal/pelvis computed tomography (CT) without contrast found a large retroperitoneal

hematoma hematoma extending over the entirety of the right psoas muscle and within the retrocolic and paracolic space. CT angiography of the abdomen/pelvis showed no bleeding source and no extravasation of the hematoma. The patient remained hemodynamically stable and remained stable with a hemoglobin level of 9 g/dL. Patient was discharged home and had no limitation to his daily functioning.

Discussion: Massive retroperitoneal hematoma is a rare complication of lumbar puncture, particularly in the patients without coagulopathy and thrombocytopenia. It is postulated that the hemorrhage may have resulted from direct trauma to a lumbar artery during the lumbar puncture procedure using the 6-inch needle. Post-LP hematomas are usually seen in patients on anticoagulants, increased age, with bleeding abnormalities, or those undergoing hemodialysis (Adyanthaya, *British Journal of Medical Practitioners* 2009; Soto-Mesa D, *Colombian Journal of Anesthesiology* 2015). There are limited case studies recording retroperitoneal hematomas post-lumbar puncture, and of those, most describe patients with the above risk factors. This case report serves to consider retroperitoneal hematomas in patients who do not display such risk factors.

311. Safety of Cerebral Angiography in Private Outpatient Clinical Setting

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Introduction: Most cerebral angiography (CA) procedures are performed in the hospital setting. Per SIR/ASNR/SNIS 2015 guidelines, acceptable success rate is 98%, with a 1-5% rate of complications requiring additional therapy. Due to procedural complexity, physicians have historically been reluctant to perform CA in the freestanding outpatient clinic. Here, we report the results of CA procedures performed in our private clinic in the past 11 years.

Methods: In this retrospective study, we collected the data on all patients who underwent CA from 2008 to 2019 in our clinic. A total of 771 consecutive procedures were analyzed. All procedures were performed by board-certified interventional neuroradiologists and senior members of Society of Neurointerventional Surgery. SIR/ASNR/SNIS 2015 guidelines were used to classify complications. Age, gender, indication, comorbidities, medication, lab results, success rate, use of closure device, Neurologic and non-neurologic complications, post-procedure hospitalization and duration of follow up were the main documented variables. Sedative dose, access route, catheter, guidewire and sheath details and use of contrast media were also recorded. Pre- and post-procedure NIHSS scores were used to evaluate possible neurologic complication.

Results: Patients' average age was 65 years, 40.3% male, 59.7% female. Indication for most procedures was aneurysm followed by carotid artery stenosis. Hypertension and diabetes were among most prevalent comorbidities. Sixty percent of patients were taking antiplatelet medication. Closure device was used in almost all patients. Overall success rate was 100%. Among all performed procedures, one neurologic complication (0.1%) was reported (TIA). Of all reported non-neurologic complications, 4 (0.6%) were classified as major (all class C) and 3 (0.4%) as minor (all class A). About 5% of patients experienced minor groin discomfort after the procedure. This places our safety outcomes well above acceptable rates. Median follow up duration was 2 weeks.

Conclusions: According to our results, CA in non-complicated cases can be safely performed outside of hospital setting by board-certified interventional neuroradiologists with high success rates and minimal complications that are comparable to MRA and CTA. Our result show that not only CA is safe in an office setting, but potentially safer than MRA and CTA when considering higher quality imaging, evaluation of collateral flow and diagnosis of many additional vascular diseases. Proper case selection for this setting plays an important role in achieving optimal results and minimizing complications.

312. Outcomes for Inter-Hospital Transfer versus Direct Admit Patients Undergoing Stroke Thrombectomy

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Background and Purpose: Mechanical thrombectomy (MT) is the standard of care for patients with large vessel occlusion and salvageable tissue. Whether the benefit of thrombectomy is maintained for patients transferred to a thrombectomy-capable center in a real-world setting remains unknown. In this study, we sought to assess clinical outcomes of MT following inter-hospital transfer.

Methods: We collected hospital course data and functional outcomes as well as time metrics for all patients who underwent MT at our institution between April 2017 and July 2018. Outcomes were compared between transferred and direct admit patients. Our outcomes measurements included National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) at 90 days. We used Mann-Whitney U and chi-square tests for univariate analysis. Then, we estimated a Generalized Linear Model with logit function to assess the relationship between transfer status and long-term functional independence (90 days mRS 0-2) controlling for age, sex, symptom-onset to groin time, IV thrombolysis, and baseline NIHSS.

Results: 96/192 (50%) patients undergoing MT were transferred and 96/192 (50%) presented directly to our institution. There was no difference in age (68 vs. 70 years, P=0.58), rate of intravenous thrombolysis (42 (43.8%) vs. 30 (31.3%), P=0.07), or baseline NIHSS (15 vs. 14, P=0.92) in the transferred and direct admit groups, respectively. Time from arrival at CSC to groin puncture was similar in both groups (80 vs. 76 min, p=0.45). While the duration from symptom-onset to groin was longer in the transferred patients (197 vs. 176 min, P=0.04), NIHSS at discharge was 5 in both groups (P=0.46), and both groups had similar length of stay (7 vs. 6 days, P=0.78). Functional independence at 90 days was observed in 40% of the patients in the transferred group compared to 36.2% in the direct thrombectomy group (P=0.143). On multivariate analysis,

transfer status was not an independent predictor of long-term functional independence (ARR 1.976, 95% CI 0.807-4.838, P=0.136).

Conclusions: In the included cohort, no difference was found in long-term functional independence between stroke patients who received mechanical thrombectomy following inter-hospital transfer compared to patients who presented directly to a thrombectomy-capable center. These findings emphasize that optimizing telestroke workflow can mitigate the adverse effects of delay during transportation for patients who present to remote hospitals in rural areas.

313. Process Improvement: Streamlining Cognitive Evaluation of Stroke Patients Treated with Mechanical Thrombectomy

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Background: Mechanical Thrombectomy (MT), either alone or in combination with the administration of intravenous recombinant tissue plasminogen activator (tPA), is the standard to achieve complete thrombolysis in acute ischemic stroke (AIS) patients with large vessel occlusion (LVO) (1). Regardless of successful recanalization, many patients experience long-term cognitive effects with the initial cerebral insult (2). Core measures for maintenance of Comprehensive Stroke Center Certification include cognitive assessment prior to discharge, but how to assess varies from institution to institution, and does not address the long-term effects of stroke on cognitive function. Although Neuropsychological Testing (NPT) is widely accepted in the evaluation of cognitive impairment (3), it is time intensive and there may be limited access to testing in the inpatient setting. We developed a protocol for including NPT at 90 days post-thrombectomy. However, we discovered that many patients were not being scheduled for appointments. The aim of this project was to identify barriers to, and subsequently improve upon, the scheduling process, so that all patients received assessment.

Methods: We conducted a single center quality improvement (QI) project to evaluate the process for scheduling and completion of NPT in all AIS patients with LVO who underwent MT. The initial intervention in February 2020 involved the Stroke Program Coordinator sharing information with the clinic schedulers and Neuropsychologists on a weekly basis to facilitate scheduling of 90 day NPT assessment. In May 2020, Stroke Fellow joined the QI project and began entering orders for follow up NPT prior to patients' hospital discharge. Three time periods were evaluated.

Results: Between January and April 2020, 37 AIS patients underwent MT for LVO. 12 patients (32%) died in the acute hospital setting. 18 of 25 patients (72%) had NPT order placed. In May 2020, 12 patients had MT. 2 patients (16%) died in the acute hospital setting. 10 patients (100%) had NPT order placed before hospital discharge.

Conclusion: A focused process of information sharing between key personnel, and a standardized process for order entry, improved the frequency with which NPT testing in post-thrombectomy patients were scheduled. The next step will be to assess completion of appointments and develop a database of NPT results.

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314. Acute Interventions for In-Hospital Stroke Patients

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Background: Thrombolysis (IVT) and endovascular therapy (EVT) are the standard of care for patients with acute ischemic stroke but are limited to those meeting specific criteria. Barriers to treatment are common for in-hospital stroke patients. Approximately 60% of inpatient strokes occur in the perioperative setting, which limits use of IVT. However, EVT may be possible. The aim of this analysis is to determine the percentage of patients with inpatient strokes who received acute intervention.

Methods: A retrospective chart review was conducted for all inpatients for whom our Brain Attack Team (BAT) was called from 2015- 2019. Data was collected regarding reason for admission, procedures completed during the admission, last known normal, timing of the BAT call, NIHSS, and details of IVT or EVT.

Results: Our sample included 201 patients, of which 110 met inclusion criteria. Mean age was 61 (46% women). Of the 110 BAT calls, 97 (88%) had ischemic strokes, of which 76 (78%) occurred in the perioperative setting. Fifteen patients had large vessel occlusions. Nine patients received acute intervention (4% IVT only, 4% EVT only, 1% IVT + EVT) with five patients (33%) with LVO receiving EVT. Last known normal was greater than 24 hours or unknown in 55% of all stroke patients.

Discussion: The majority of inpatient BAT calls were diagnosed with ischemic stroke however only 8% received IVT+/- EVT. A major barrier to thrombolysis specifically was recent surgery. Delayed symptom recognition was a significant limitation for both IVT and EVT. The low rate of EVT (4.5%) is partially explained by most of the patients being seen prior to late window trials being published. Future studies should address whether EVT use increases with the more widespread use of perfusion imaging in later time windows.

315. Bilateral Thalamic Venous Edema Associated with Unruptured Arteriovenous Malformation Corrected with Endovascular Therapy: A Case Report and Literature Review

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Arteriovenous malformations (AVMs) are abnormal arteriovenous shunts that can evolve with an unclear pathophysiological mechanism; their manifestations are frequently derived from hemorrhage or ischemia due to a steal phenomenon and, exceptionally, from edema due to venous congestion (1). We present the case of a 51-year-old male patient with a history of diabetes mellitus and dyslipidemia who was evaluated by confusion, headache and seizures. On his neurological examination, he was found alert, disoriented, with bradypsychia, bradylalia, mild dysdiadochokinesia, without another abnormal findings. A brain MRI, was performed, in which bilateral thalamic hyperintensities in the right parasagittal region were found. The cerebrospinal fluid showed hyperproteinorraquia and ruled out infection. In the absence of a clear etiology, a cerebral arteriography to rule out vascular involment was performed, in which a choroidal fistulous pial AVM is observed with main afferences from the posteromedial choroidal artery branches with the presence of venous aneurysms and hypertension in the deep venous system. During the inpatient stay, the patient presented an abnormal gait and a severe impaired consciousness. It is considered that the clinical picture is explained by bilateral thalamic edema due to a disorder of venous drainage, reason why he is taken to emergency endovascular therapy. His clinical and radiological manifestations improved dramatically after correction of the arteriovenous malformation. The clinical presentation in our case report is very rare and interesting. The findings were a choroidal AVM of the midline without rupture, which produced subacute and progressive bi-thalamic edema, which is secondary to venous congestion that altered the normal venous drainage of the thalamus. This produced the clinical manifestations of the patient. Few similar cases have been identified in the literature (2), making it a clinical challenge to quickly identify this entity for teamwork between neurology and a neurointerventional surgeon.

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Movement Disorders

452. *APOE* Genotype Regulates Pathology and Disease Progression in Synucleinopathy

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APOE e4 genotype increases risk of dementia in Parkinson disease (PDD) and dementia with Lewy bodies (DLB) but the mechanism of this association is not clear, as patients with PDD and DLB often have a mixture of alpha-synuclein (aSyn), amyloid-beta (Abeta), and tau pathologies. *APOE* e4 exacerbates brain Ab pathology, as well as tau pathology, but it was not previously clear whether *APOE* genotype independently regulates aSyn pathology. In this study we generated A53T aSyn transgenic mice (A53T) on *Apoe* knockout (A53T/EKO), or human *APOE* knock-in backgrounds (A53T/E2, E3, E4). At twelve months of age, A53T/E4 mice accumulated higher levels of detergent-insoluble phosphorylated aSyn in the brainstem compared to A53T/EKO and A53T/E3; levels in A53T/E2 mice were undetectable. By immunohistochemistry, A53T/E4 mice displayed a higher burden of phosphorylated aSyn inclusions and reactive gliosis compared to A53T/E2 mice. Gene expression analysis indicated that glial-mediated inflammation correlated strongly with the presence of aSyn pathology, but did not directly correlate with *APOE* genotype. Expression of genes associated with myelination was negative correlated with aSyn pathology but positively correlated with *APOE2* genotype. Behavioral analysis showed delayed onset of motor deficits in A53T/E2 mice, and A53T/E2 mice survived longer compared to other *APOE* genotypes. In a complementary model of aSyn spreading, striatal injection of aSyn pre-formed fibrils resulted in increased accumulation of aSyn pathology in the substantia nigra of A53T/E4 mice compared to A53T/E2 and A53T/EKO mice. Among human patients with PD, *APOE* e4/e4 individuals showed the fasted rate of cognitive decline, while *APOE* e2/e2 individuals remained stable over time. Our results demonstrate that *APOE* genotype directly regulates aSyn pathology independent of its established effects on Abeta and tau and suggest that *APOE* e2 may confer protection against aSyn aggregation and neurodegeneration in synucleinopathies.

453. Phantom Limb Pain Associated with Restless Limbs Syndrome: A Dopamine Responsive Disorder

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Restless Limbs Syndrome (RLS) is a common but underdiagnosed condition of unknown etiology contributing to chronic pain, insomnia and distress. It is known to respond to both dopaminergic and gabergic agents. Phantom limb pain, also of unknown etiology, shares some clinical features with the quality of dysesthetic pain and paresthesiae experienced in RLS. Between 2012-2015 we studied 1000 patients with IRLSSG criteria for RLS and have reported a strong association with migraine headaches and bruxism (up to 51% had the full triad). During this period we encountered 3 patients with chronic, refractory Phantom Limb Pains with clinical features suggesting RLS including: nocturnal predominance of symptoms and insomnia (3 of 3), migraine headaches (2 of 3), bruxism (2 of 3), and involvement in non-amputated limbs (2 of 3). Symptoms improved or resolved on pramipexole (2 of 3) and gabapentin (1 of 3) allowing discontinuation of chronic pain medications including narcotics. In 1 of 3 improvement persisted after discontinuation of the dopamine agonist.We report these 3 cases and review prior case reports of phantom limb pain and RLS

from the literature.We believe these cases, taken together, suggest that RLS may be the etiology of some or most cases of phantom limb pain, suggest that dopamine agonists should be trialed in this condition, and support a central etiology of both conditions.

454. A Multidisciplinary, Innovative Care Model for Dystonia - One Center's Unique Structure of Comprehensive and Individualized Treatment

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Introduction: Our vision is to provide the highest quality of care to those with dystonia in our service area and beyond. We are dedicated to offering comprehensive and individualized treatment to our patients and their families. The Center's goal is to be a national leader in the field by offering innovative care, advanced treatment, cutting edge clinical research, and compassionate home and community services.

Materials and Methods: We have six movement disorders neurologists and seven advanced practitioners in our three locations, and we are sustaining our unique and ingenious preceptorship model of care. All patients see a Movement Disorders specialist at every visit, whereas patients in most other institutions see an advanced practice provider only, and an MD or DO on every second or third visit. This is fundamental to our practice, as we are in a highly subspecialized field, administering botulinum toxins and caring for issues where it is crucial to preserve the long term patient-physician relationship. Patients also have access to a psychiatrist, social worker, and a neuropsychologist, as well as rehabilitation services, integrative medicine and wellness programs. Our center also offers naturopathic medicine options and integrative medicine practices for dystonia such as acupuncture, yoga, massage therapy, Tai Chi, Reiki and Qigong.

Results: In 2019, we provided 267 acupuncture and 193 massage therapy treatments to our patients who had been referred to the various Integrative Medicine services. In the first two months of 2020, we were able to begin offering patients naturopathic consultations and have completed 13 visits to date. We continue to capture data to establish the efficacy outcomes of massage therapy in combination with botulinum toxin injections in the management of cervical dystonia. We are also collecting long-term data on the use of naturopathic options for the treatment of dystonia.

Discussion: With the unique breadth of clinical expertise available to all of our patients, regardless of the location where they are seen, we are providing truly integrated, personalized, and comprehensive care for dystonia. With specialty services simply "down the hall" in our locations, coordination of services is seamless and convenient for our patients. Our personalized management approach to dystonia have lead to improved outcomes and could serve as a model for other centers around the world.

455. Increased Serum Neurofilament Light Chain Levels in Spinocerebellar Ataxia

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Background: The spinocerebellar ataxia (SCA) is heterogeneous group of inherited diseases which commonly presents with progressive ataxia. As serum neurofilament light chain (NfL) has been known as a promising biomarker in various neurodegenerative diseases, we aimed to evaluate serum NfL as a biomarker indicating neuronal damage in SCAs.

Methods: We reviewed patients diagnosed with SCA in outpatient clinic of Seoul National University Hospital department of neurology, between May 2019 and September 2019. We reviewed the demographic data, and clinical characteristics, evaluated baseline clinical severity by using Scale for the Assessment and Rating of Ataxia (SARA) at their first visit. Serum NfL was measured by electrochemiluminescence (ECL) immunoassay.

Results: Forty-nine patients with SCA were reviewed and measured serum NfL level. Serum NfL was median 109.5 pg/mL (17.9-388.5 pg/mL) in SCA patients, and was higher than controls (median 41.1 pg/mL, 20.8-197.9 pg/mL). Within SCA patients, there was positive correlation in serum NfL level with trinucleotide repeat number (0.469, p-value = 0.001), disease period (r = 0.341, p-value = 0.019), and baseline SARA scale (r = 0.371, p-value = 0.033). However, disease onset did not have significant correlation with serum NfL (r = -0.013, p-value = 0.934). Within different SCA types, the trinucleotide repeat number and serum NfL did not have significant correlation.

Conclusions: We found that serum NfL elevates in SCA patients, and correlates with clinical severity. Further studies with larger longitudinal cohorts of SCA patients with different SCA types, including patients with pre-clinical stage, is required to investigate serum NfL as reliable biomarker and screening method of SCA.

456. Spinal Segmental Myoclonus Associated with Episodes of Autonomic Dysreflexia in an Individual Living with Tetraplegia: A Case Report

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Background: Autonomic dysreflexia is a relatively common and potentially life-threatening secondary complication after spinal cord injury (SCI) at levels from C1 to T6. This unique case report describes, for the first time, a movement disorder associated with episodes of autonomic dysreflexia (AD) in an individual living with tetraplegia.

Case Presentation: A 60 year-old, male sustained a C4 complete (AIS-A) tetraplegia after a diving accident 30 years ago. He subsequently developed several secondary complications of his SCI including: neurogenic bladder, recurrent urinary tract infections, neurogenic bowel, orthostatic hypotension, AD, neuropathic pain, spasticity, pressure sores, sublesional osteoporosis, heterotopic ossification, sleep-related breathing disorder, and mood disorder. He then developed intermittent jerk movements affecting multiple muscles of the abdominal wall, low back and thighs that started during his hospitalization for treatment of urosepsis 7 years after the SCI onset. He was eventually diagnosed with spinal segmental myoclonus on the basis of clinical and electrophysiological assessments (video to be presented). Neurophysiological assessments revealed that his spinal segmental myoclonus generates from L3-L4 levels. His myoclonus typically lasts from minutes to hours. The episodes of myoclonus are often associated with sweating, hyperthermia and increase in blood pressure (systolic blood pressure occasionally reaches levels above 200 mmHg). His myoclonus had partial response to cannabis and clonazepam. The episodes of myoclonus further improved after he underwent colostomy for complicated neurogenic bowel 9 years after SCI onset, even though his myoclonus worsened 2 years later. More recently, his myoclonus has significantly improved since the management of his atonic neurogenic bladder had changed from use of condom catheter to intermittent catheterization every 8 hours.

Discussion and Significance: The temporal link between the myoclonus onset and the presence of common triggers for autonomic dysreflexia suggests the possibility that the former is associated with the latter. Moreover, the concomitant occurrence of myoclonus and signs of AD in several occasions reinforces the potential association of this movement disorder and AD. While the current first line pharmacological therapy for spinal myoclonus was only partially effective, the elimination of common triggers for AD according to current PVA Clinical Practice Guidelines was sufficient to provide further control his movement disorder. Further investigations are necessary to elucidate the pathophysiology of the association of myoclonus with AD.

457. Nilotinib Alters microRNAs That Regulate Specific Autophagy and Ubiquitination Genes in the CSF of Individuals with Parkinson's Disease

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We evaluated the effects of nilotinib on microRNAs in the cerebrospinal fluid (CSF) of Parkinson's disease patients. CSF was collected as part of an open label phase I (12 participants, 6 months treatment)) and phase II randomized, double-blind, placebo-controlled study with 75 participants randomized 1:1:1 into placebo, 150 mg or 300 mg nilotinib groups. Nilotinib versus placebo was taken orally once daily for 12 months. Our preclinical data demonstrated that the principal effects of nilotinib is clearance of misfolded proteins, including hyper-phosphorylated tau and oligomeric alpha-Synuclein via autophagy. Nilotinib increases the levels of key autophagy proteins like parkin, beclin-1, light chain protein (LC3-I/II), P62, and autophagy like proteins (ATGs) in animal models of neurodegeneration. Next generation whole-genome sequencing of microRNAs in the CSF demonstrated that nilotinib significantly increases (multiple fold with False Discovery Rate $p<0.001$) microRNAs that specifically regulate the expression of autophagy and ubiquitination genes in individuals with PD. No effects were detected on genes that regulate tyrosine kinases, which are the likely protein targets of nilotinib. These data provide robust evidence that nilotinib effects on misfolded protein clearance is via autophagy. CSF microRNA sequencing is a valid biomarker of nilotinib effects on autophagy in a definitive phase III study to investigate nilotinib in PD and other neurodegenerative diseases.

458. Variants in Saposin D Domain of Prosaposin Gene are Linked to Parkinson's Disease

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Recently, the genetic variability in lysosomal storage disorders (LSDs) has been implicated in the pathogenesis of Parkinson's disease (PD). We found that variants in prosaposin gene (*PSAP*), a rare causative gene of various types of LSDs, are linked to PD. Genetic mutation screening and whole-exome sequencing study identified three pathogenic mutations in *PSAP* saposin D domain from three families with autosomal dominant PD. A case-control association study revealed that two variants in the intronic regions of the *PSAP* saposin D domain (rs4747203 and rs885828) in

sporadic PD had significantly higher allele frequencies in a combined cohort of Japan and Taiwan. Skin fibroblasts or induced pluripotent stem cell (iPSC)-derived dopaminergic neurons, which were obtained from PD patients with *PSAP* saposin D domain mutations, presented abnormalities in autophagy-lysosomal pathway, alteration in intracellular localization of PSAP, and aggregation of alpha-synuclein. In mice, a *Psap* saposin D mutation caused a progressive motor decline and dopaminergic neurodegeneration. Our data provide novel genetic evidence for the involvement of the *PSAP* saposin D domain in PD.

459. Phantogeusia in Parkinson Disease Responsive to Sweet Cereals

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Background: Elimination of gustatory hallucinations (phantogeusia) with manipulation of breakfast cereal has not heretofore been reported.

Case History: A 59-year-old right-handed woman with Parkinson disease presented with a 4 years history of a bitter, sour, and sweet tastes on her entire tongue. Over a year, the persistent taste became limited to bitter and sours but not sweet. Eating cereals markedly masked the taste which made her constantly crave cereals. Before cereal her persistent taste was 7-8/10 in intensity and with cereal it was reduced to 2-3/10 in intensity. The intensity of phantogeusia reduced from 5/10 to 0/10 with Sugar Pops, 5/10 to 0/10 with Apple Jacks, and 7/10 to 0/10 with Fruit Loops. After occluding nostrils with nose clips, phantogeusia dropped from 7/10 to 0/10 with Sugar Pops, Apple Jacks, and Fruit Loops.

Result: Abnormalities in Neurological examination: Mental status examination: Bradyphrenic. Mood sad. Cranial Nerve (CN) examination: CN lll, lV, Vl: saccadization of horizontal eye movements. Hypomimetic. Decreased blink frequency. Motor Examination: Bradykinetic. Pill rolling tremor in right hand. 1+ cogwheel rigidity in left upper extremity. Gait: 2+ retropulsion. Chemosensory testing: Olfaction: Alcohol Sniff Test: 6 (anosmia). Phenylethyl Alcohol Threshold Testing: left -2.5 (hyposmia), right > -2.0 (anosmia). 4 Item Pocket Smell Test: 3/4 (hyposmia). Retronasal Smell Index: 10 (normosmia). Gustatory testing: Propylthiouracil Disc Taste Test: 10 (normogeusia). Taste Threshold: normogeusia to NaCl, Sucrose, HCl, Urea, and PTC. Other: DOPAPET: positive for Parkinson disease.

Conclusion: Diminutions in the phantogeusia in response to manducating the cereal suggest chemosensory origin for the problem. Lack of response to Shredded Wheats but response to sweetened cereals suggests that it's not primarily due to effects of chewing alone but rather due to the sensory components of cereal. The absence of reduction with elimination of retronasal smell with nose plugs indicates that the effect is not olfactorily mediated but rather true taste. Furthermore, the lack of response to Shredded Wheat as opposed to sweetened cereal suggests that it is not just the somesthetic/ texture sensation or the origin for the effects but rather the impact of the different components of the flavor of cereals, most noticeably sweet component. This concept is further amplified with response to the multitude of sweet cereals. These results suggest that phantogeusia may respond to sweet food or sweet gum which has fewer side effects than pharmacological intervention.

460. Critical Glial Role for Parkinson's Disease Risk Genes in Controlling Alpha-Synuclein Toxicity

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Parkinson's disease (PD) is estimated to be approximately 30% heritable, and genome wide association studies (GWAS) have revealed numerous loci associated with risk of PD. The majority of genes implicated by GWAS are expressed in glia, suggesting that glia play a role in development of PD. The role of individual glial risk genes in PD is unknown, however. We developed a Drosophila model of alpha-synucleinopathy by expressing human alpha-synuclein in neurons. We then performed a candidate genetic screen, knocking down 14 well-validated PD risk genes in glia and measuring the effect on locomotion in order to identify glial modifiers of the alpha-synuclein phenotype. We then used an array of tools available in Drosophila to identify pathways influenced by the modifiers. 6 out of 14 GWAS candidate genes enhanced the neuronal alpha-synuclein induced motor phenotype when knocked down in glia. 4 of these were selected for further study due to the amplitude of their effect and confirmation with an independent RNAi line: GAK, LRRK2, RIT2, and VPS13C. Knockdown of each gene exacerbated neurodegeneration, and we identified specific pathways affected by each gene. These results suggest that some PD risk genes exert their effects partially through glia. Further, this study provides proof of concept that our Drosophila alpha-synucleinopathy model can be used to study glial modifier genes, paving the way for future large unbiased screens to identify novel glial risk factors that contribute to PD risk and progression.

461. A Novel Small Molecule Tyrosine Kinase Inhibitor (GUtinib) Preferentially Targets Discoidin Domain Receptors and Reduces Toxic Proteins in Neurodegeneration

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Tyrosine kinase inhibition (TKi) is a potential new strategy to target misfolded protein degradation in neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and Lewy Body Dementia (DLB). Our laboratory demonstrated that multi-kinase inhibitors like nilotinib and bosutinib are optimal agents since they target both Abl and Discoidin Domain Receptors (DDR1/2) and Abl and SRC tyrosine kinases, respectively. These two agents are currently in phase II in DLB (nilotinib and bosutinib), PD and AD (nilotinib). Profiling the tyrosine kinase targets of several FDA-approved drugs shows that agents with high potency to Abl alone are ineffective and cannot clear toxic proteins, but

a multikinase inhibition like Abl/SRC and DDRs is optimal for misfolded protein clearance. Here we report a novel tyrosine kinase inhibitor (GUtinib) that has the highest specificity to DDR1/2 and exhibits a high efficacy to clear human alpha-Synuclein, amyloid-beta and hyper-phosphorylated tau in several animal models of neurodegeneration. Our data indicate that GUtinib preferentially targets DDR1 and 2, but not Abl, and induces autophagy at very low concentrations and higher efficacy than other multikinase inhibitors. Further toxicology experiments will be conducted to obtain pre-investigational new drug (pre-IND) status, and if the safety of GUtinib is acceptable this agent will be tested in first-in-human early development clinical trials.

462. Efficacy and Safety of the T-Type Calcium Channel Modulator CX-8998 in T-CALM, a Randomized, Double-Blind, Placebo-Controlled, Phase 2a Trial in Participants with Essential Tremor

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Introduction: Essential tremor (ET) is possibly the most prevalent movement disorder in adults. CX-8998 is a potent, selective, state-dependent modulator of T-type calcium channels, which are mediators of subthreshold oscillations and excessive rhythmicity in pathophysiologic states found in tremor, and are highly expressed in functional tremor network regions. The objective of T-CALM (NCT03101241) was to determine the efficacy and safety of CX-8998 in participants with moderate to severe ET.

Methods: Adults (N=95) with ET who scored ≥15 on The Essential Tremor Rating Assessment Scale performance subscale (TETRAS-PS) were randomized to receive CX-8998 (titrated to as high as 10 mg twice daily [BID]) or placebo for 28 days. Use of a single concomitant anti-tremor medication other than primidone was allowed. Clinical efficacy assessments were collected at baseline, day 15, and day 28. Changes from baseline to day 28 on TETRAS-PS and the activities of daily living subscale (TETRAS-ADL) were evaluated using analysis of covariance in the full analysis set, which included all participants who received study drug and had baseline and ≥1 post-baseline assessments. A prespecified analysis evaluated outcomes in subgroups defined by baseline TETRAS-PS scores at or below (less severe) and above (more severe) the median score of 22.5.

Results: TETRAS-PS scored by independent video raters (primary endpoint) did not reach significance (P=0.696). TETRAS-PS rated by investigators, TETRAS-ADL, TETRAS total score (sum of investigator-rated TETRAS-PS and TETRAS-ADL), and Clinical Global Impression of Improvement were improved at day 28 (all nominal P values <0.05). For investigator-rated TETRAS-PS, least squares (LS) mean differences from placebo (95% confidence interval [CI]) in change from baseline to day 28 were −1.2 (−3.1 to 0.6) in the less severe subgroup (n=44) and −3.5 (−7.4 to 0.4) in the more severe subgroup (n=39). For TETRAS-ADL, LS mean differences from placebo (95% CI) in change from baseline to day 28 were −1.6 (−4.7 to 1.4) in the less severe subgroup and −5.8 (−11.2 to −0.5) in the more severe subgroup. Adverse events were mostly mild to moderate.

Conclusions: The study achieved proof-of-concept in ET and provided information on future study design parameters. For participants with more severe tremor at baseline, the treatment effect with CX-8998 may be larger relative to those with less severe baseline tremor (at the same doses).

Support: Jazz Pharmaceuticals

463. HIV Protease Inhibitors Activate the Integrated Stress Response and Correct Diverse Dystonia Phenotypes in Mouse Models

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Current orally available drug treatments for dystonia suffer from limited efficacy, narrow therapeutic window and lack of disease modification. To identify novel therapeutics, we performed drug library screen using a high-throughput assay which tracks protein mislocalization due to the causative TOR1A mutation in a monogenic form of the disorder, DYT-TOR1A dystonia (n. ΔGAG, p. ΔE, DYT1). The HIV protease inhibitor, ritonavir was among the top 18 hits out of a total 2816 compounds in the NIH pharmaceutical collection. To determine the therapeutic potential of ritonavir, we tested its performance in 2 phenotypes of the etiological DYT1 mouse model of dystonia (Tor1a$^{+/\Delta GAG}$). Acute ritonavir treatment of brain slices restored the normal firing rate response to the D2R agonist, quinpirole, in striatal cholinergic interneurons. Secondly, in vivo ritonavir treatment during a brief early developmental window led to long-lasting normalization of DTI MRI signals in adulthood.

Mechanistically, we find that ritonavir acts through potentiation of the Integrated Stress Response, a pathway recently implicated in multiple forms of dystonia. These preclinical study results show great promise for the development of ritonavir or its derivatives into a first-in-class treatment for dystonia with disease modifying potential. Because the EC_{50} of ritonavir in dystonia assays is orders of magnitude higher than current clinically approved uses, translation to human populations will require further understanding of molecular target, formulation, dosing and safety issues.

464. Objective Dystonia Identification Helps Elucidate Dystonia Pathophysiology

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Introduction: Dystonia is debilitating but difficult to diagnose. The diagnostic gold standard remains subjective identification by expert consensus. However, objective dystonia identification is necessary to study its pathophysiology in animal models. Many mouse models of genetic dystonias display abnormal striatal cholinergic interneuron (ChI) excitation, but few display subjectively dystonic features. Therefore, it unknown whether striatal ChI pathology actually causes dystonia.

Methods: We aimed to: 1) Derive an objective dystonia identification method from clinical subjective diagnosis; 2) Use this method to identify dystonia in human and animal subjects; 3) Use this method to examine whether striatal ChI excitation causes dystonia. Qualitative thematic analysis was used to extract features cited by pediatric movement disorders specialists when diagnosing dystonia in gait videos of children with spastic cerebral palsy, thus converging on features specific to dystonia and not spasticity. Deep neural network transfer learning-based pose-estimation (DeepLabCut) was then used to quantify these features in patient videos, mice after neonatal global hypoxic brain injury, and mice following striatal ChI excitation using designer receptors exclusively activated by designer drugs (DREADDs). For striatal ChI excitation, choline-acetyltransferase Cre-positive and negative (control) mice were injected with AAV8-hSyn-DIO-hM3d (Gq)-mCherry in the bilateral dorsal striatum. Three weeks later, the DREADD ligand clozapine-N-oxide (CNO) was given to all mice acutely (1mg/kg intraperitoneal injection) then chronically (1mg/kg/day orally via drinking water for two weeks), noting that only Cre-positive mice express excitatory Gq DREADDs and undergo striatal ChI excitation.

Results: Experts cited unilateral foot adduction variability more frequently when identifying dystonia (Chi square, $p<0.0001$, n=40). Using DeepLabCut, this was quantifiable as higher foot angle variability during gait in children with dystonia (per expert consensus) compared to those without (t-test, p=0.002, n=30). Comparably, mice demonstrated greater paw angle variability during gait following neonatal hypoxic injury compared to sham-injured littermates (t-test, p=0.02, n=52). Higher paw angle variability tracked with higher arousal-dependent co-contraction measures, which we previously described as a dystonia analogue (Aravamuthan et al., *Neurobiol. Dis.*, 2020). Finally, mice demonstrate increasing paw angle variability with ongoing striatal ChI excitation (two-way ANOVA, p=0.03, n=17) but no change in paw angle variability following only acute CNO administration.

Conclusion: Objective quantification of a clinically-derived dystonic motor feature facilitated our determination that chronic, but not acute, striatal ChI excitation yields dystonic behavior in mice. Therefore, objective dystonia identification, as outlined here, could aid clinical dystonia diagnosis and its study in animal models of disease.

465. Disparities in Access to Care and Research Participation in Advanced Parkinson's Disease: Differences between a Home Visit Study and Outpatient Clinic Population

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Objective: To describe sociodemographic differences between individuals with advanced Parkinson's Disease (PD) still receiving care in an outpatient clinic vs. those enrolled in an interdisciplinary home visit study.

Background: Individuals with PD from underrepresented minority backgrounds face disparities in access to expert neurologic care. Such disparities also persist in PD research participation, sometimes attributed to mistrust and stigma. As minority patients become homebound, they are further estranged from care and research representation. We launched an interdisciplinary home visit study to extend continuity of care to homebound individuals with advanced PD. Here, we seek to identify sociodemographic differences between home visit (HV) participants and the outpatient (OP) clinic population from which they were recruited to determine whether disparities in care and research enrollment among minority patients persist with this patient-centered, care-focused intervention.

Design/Methods: Cross-sectional study comparing individuals with advanced PD—Hoehn & Yahr stage $\geq$3—drawn from a single movement disorders center between 2017-2019. We conducted a chart review for demographic information and used t-tests or Wilcoxon signed-rank tests as appropriate to assess population differences.

Results: The HV population is significantly older (n = 58 HV, 1015 OP; mean age 78.4 (SD 7.5) vs. 75.0 (SD 9.2), respectively, p = 0.002) and includes nearly twice the percentage of minority patients (26.3% non-Caucasian vs. 14.7% non-Caucasian in OP, p = 0.02). As expected, HV had worse PD severity, with 62.1% stage 4 and 17.2% stage 5, vs. 28.6% and 11.0% of OP, respectively ($p<0.0001$).

Conclusions: The proportion of minority patients with advanced PD enrolled in a home-based study is significantly

greater than that receiving care in the OP setting from which they originated. This suggests that social determinants of health may contribute to advanced PD patients from underrepresented minorities becoming lost to follow-up earlier than white patients. We are actively comparing our homebound population with matched controls from a longitudinal national registry to determine the generalizability of this finding. Our results suggest that despite their advanced age, disease, and homebound status, this population is amenable to research participation. Ultimately, continued access to care poses a large but surmountable hurdle to research participation for minority patients.

466. Optimizing Patient-Specific Computational Models of DBS Using Intraoperative Electrocorticography

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Objective: Biophysical computational models of deep brain stimulation (DBS) are frequently used in clinical and research applications yet direct validations of model predictions regarding the spread of stimulation are lacking. Our goal is to optimize and validate patient-specific DBS models using cortical evoked potentials recorded in patients with Parkinson disease undergoing DBS surgery.

Methods: We measured antidromic evoked potentials over the primary motor cortex using a temporary subdural strip electrode to quantify activation of cortico-subthalamic hyperdirect pathway (HDP) by subthalamic DBS. We built detailed biophysical computational models to estimate the spread of stimulation around the DBS electrode using novel driving-force predictors. Patient imaging specified DBS electrode locations and a published anatomical atlas defined HDP course through the subthalamic region. We compared HDP activation predicted by the model (i.e., the percentage of atlas pathway streamlines activated by given DBS setting) to the amplitude of the recorded cortical potentials evoked by the same DBS settings, using Pearson correlation (R^2). DBS settings varied in active contact configuration, amplitude and pulse width (frequency was set at 10 Hz). Model axonal diameters and lead localization techniques were systematically adjusted to maximize R^2 in the optimization (training) patient cohort.

Results: We included 7 patients in the optimization cohort and 3 patients in the validation (testing) cohort. On average, 31 DBS settings were applied per patient (range 18-41). In the optimization cohort, the final R^2 after model parameter adjustment was 0.73 for HDP activation (range 0.54-0.88). The same model parameters were applied in the validation cohort, and the resulting R^2 was 0.64 (range 0.56-0.69).

Conclusions: We demonstrate that optimized computational models can predict hyperdirect pathway activation in the subthalamic region with high accuracy (R^2 consistently greater than 0.5). Future studies should investigate whether patient-specific, driving-force models may have utility for efficient selection of optimal DBS settings in clinical practice.

467. The Molecular Integration in Neurological Diagnosis Parkinson's Disease Observational Study: MIND-PD

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Objective: To describe the clinical characteristics and the frequency of *GBA* and *LRRK2* variants in the Parkinson's disease (PD) patient population at The University of Pennsylvania Parkinson's Disease and Movement Disorders Center (PDMDC).

Background: Traditionally, observational studies in PD research have focused intensely on small numbers of dedicated research participants. This approach is valuable for many research questions; however, it falls short in capturing the molecular and genetic variability across the PD spectrum. The MIND Initiative was developed to characterize the genetic and molecular features of PD by approaching every patient in a large academic movement disorders center at The University of Pennsylvania. This approach allows for greater inclusion in research studies in PD, and expands biobanking of blood and DNA to capture an entire PD clinic population.

Methods: This is an inception cohort study of participants with a clinical diagnosis of PD followed at the PDMDC. Each participant completes a brief clinical questionnaire and DNA is isolated from a blood sample. Optional permissions for access to the medical record, future recontact about other studies, and the use of samples for additional studies are asked of each participant during the informed consent process. Targeted genotyping for eight *LRRK2* and four *GBA* variants is performed for all participants. Plasma and DNA are banked for future research.

Results: Between September, 2018, and December, 2019, 652 PD subjects were enrolled, with a median age of 69 (IQR 63-75), and median disease duration of 5.4 (IQR 2.5-9.9) years. Among 704 screened and approached to participate, 28 patients (3.9%) declined participation, and 24 patients (3.4%) did not meet the eligibility criteria of having a PD diagnosis. One-hundred percent of participants opted to allow access to their medical record and future recontact about other research studies, while >99% opted to allow the use of their samples for additional studies. Clinical questionnaires were collected for 99% of participants and common motor and non-motor complications of PD are described. *GBA* variants were identified in 39 participants (6.0% of whole cohort), *LRRK2* variants in 16 participants (2.5% of whole cohort). Two participants carried a *GBA* and *LRRK2* variant (0.3% of whole cohort).

Conclusion: This is the first report to demonstrate the clinical and genetic characteristics of a whole-clinic PD population at an academic center.

468. Acquired Movement Disorders Secondary to Tumefactive Virchow Robin Spaces

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Perivascular spaces, commonly known as Virchow-Robins spaces, are interstitial cystic spaces filled with cerebrospinal fluid (Al Abdulsalam, World Neurosurgery, 2018). Traditionally, these spaces are asymptomatic and benign, but these spaces can expand into giant tumefactive PVSs (GTPVSs) compressing nearby structures causing neurologic conditions and hydrocephalus (Kwee, Radiographics, 2007). We present the rare case of a nonsyndromic pediatric patient with an acquired, unilateral movement disorder secondary to GTPVS. 17-year-old male with a history of congenital hypothyroidism, that presents to the movement disorders clinic with chronic, nonprogressive left upper limb tremors. The patient first experienced symptoms at age 11. At that time, he experienced excessive drowsiness and developed left upper extremity tremors and abnormal extraocular movements with a compensatory head tilt. MRI revealed a large cystic lesion at the right midbrain and thalamus. Biopsy revealed a GTPVS with mild hydrocephalus. There was no evidence of an infectious etiology and no further neurosurgical interventions were pursued. Annual head MRIs have demonstrated no evolution of the GTPVS.Examination revealed left eye had an elevated gaze when compared to the right, with skewed lateral left and right gaze, intermittent horizontal, and rotary nystagmus. At rest, no abnormal movements were noted. With posture in wing-beating position, left upper extremity proximal tremor was noted. Mild bradykinesia in the left upper and lower extremity. In addition, mild dystonia of left hand which is evident only with action. Left-sided mild ataxia and impaired tandem gait were observed. While holding his left forearm with his right hand the finger-to-nose testing showed a marked decrease in ataxia. The GTPVS in this patient is located predominantly in the right midbrain and thalamus, which correspond to the laterality of symptoms. Unilateral dystonia, ataxia, tremor, as well as skew deviation and torticollis, have remained largely unchanged over the years, and trials of carbidopa/levodopa have been unsuccessful in reducing symptoms. This case highlights that dilated perivascular spaces are not always benign entities and can result in complex neurologic presentations, even in pediatric patients.

469. Levetiracetam for Sleep Disturbances in Huntington's Disease

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Introduction: Huntington's Disease (HD) is a neurodegenerative disorder that is identified by a progressive decline in motor function and cognition, along with behavioral changes. HD has a known association with sleep disorders as well. Current treatment modalities do not provide adequate relief of sleep disturbances, and there is a need for more effective treatment. The use of levetiracetam in HD has been anecdotally considered for many years, but there is no proven clinical evidence for its efficacy in sleep disorders related to HD. We completed a systematic review of the literature to assess if levetiracetam and its analog piracetam are useful in promoting sleep efficiency in HD patients.

Methods: A review of Pubmed and Embase databases was completed using the following combination of key terms: Huntington's Disease, Levetiracetam, Keppra, Sleep Disorders and Piracetam.

Results: A total of 330 articles were found after the removal of duplicates. Twenty-nine articles were found relevant to this study. Although there is increasing evidence that levetiracetam and piracetam are useful when treating cognitive decline and memory deficits in neurodegenerative diseases such as Alzheimer's, there is scant evidence for their in HD. Additionally, although levetiracetam has shown evidence of improved sleep efficiency and overall sleep time in healthy patients, there are few studies on how it may affect sleep in HD patients. Similar studies with piracetam in animal models demonstrated improved sleep efficiency as well. There is no published literature on the use of levetiracetam as a treatment for sleep disorders in HD. There is literature describing the use of levetiracetam as an alternative for chorea in HD, but it inadvertently led to secondary parkinsonism with prolonged use. Similarly, piracetam's use in HD resulted in the worsening of chorea.

Conclusion: Currently, enough clinical evidence does not exist to support the use of levetiracetam or its analog piracetam in HD patients suffering from sleep disorders. Levetiracetam may provide some clinical benefits in promoting sleep efficiency, but additional research to understand the long-term effects of this medication on HD patients is required.

470. Association between Fatigue and Motor Progression in Parkinson's Disease in Southern Chinese

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Background: Parkinson's disease (PD) is a common movement disorder characterized by bradykinesia, rigidity and resting tremor. PD symptoms were divided into two parts, motor symptoms non-motor symptoms. Non-motor symptoms vary from people to people, and there are several different non-motor symptoms in PD, such as autonomic symptoms and fatigue. And fatigue is commonly seen, disabling but easily ignored symptom in PD. But relationship between fatigue and disease progression has not been clarified. It is beneficial to aware the progression of PD, which is useful for management and nursing.

Objectives: The aim was to investigate whether fatigue could predict the development of motor symptoms of PD in the southern Chinese population.

Methods: 246 PD patients were recruited. All patients were evaluated by Fatigue Severity Scale (FSS), Hamilton anxiety rating scale, Hamilton depression rating scale and Unified PD Rating Scale provided by movement disorders society (MDS-UPDRS) at baseline. MDS-UPDRS were re-

evaluated after 2 years. Univariate regression analysis and multivariate regression analysis were used for statistical analysis.

Results: FSS scores were associated with total score and subparts of MDS-UPDRS. (Total: p=0.039; p=0.030, adjusted; Part III: p= 0.022; p=0.016, adjusted).

Conclusions: Our study found that subjective fatigue severity score was associated with the progression of the motor function of Parkinson's disease. Therefore, fatigue could predict the progression of PD. And larger multicenter studies are warranted.

471. Deficits in Postural Stability in Parkinson's Disease Patients with Freezing of Gait

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Objective: To determine if postural sway is differentially affected in Parkinson's Disease (PD) patients with and without freezing of gait.Introduction: Freezing of gait (FOG) is a phenomenon in which PD patients feel their feet are "stuck to the ground" while ambulating. As balance circuitry is involved in gait control, it has been suggested that increased postural instability may contribute to the increased risk of falls in freezers. Prior small cross-sectional studies have reported impaired mediolateral (ML) sway in PD FOG subjects. For appropriate risk stratification and medical management, understanding the relationship between freezing and balance is necessary.

Methods: After consent and IRB approval, 35 PD patients with (FOG) and 33 without (noFOG) gait freezing, and 27 healthy controls (HC) were enrolled. The subjects stood on an instrumented gait mat (Protokinetics) as still as they could for 30s with eyes open (1) with feet together (quiet stance) and (2) in tandem stance. Center of pressure (COP) measurements were recorded at 120Hz and analyzed for anterior-posterior (AP) and medial-lateral (ML) movement. Variance, Coefficient of variation (%CV), total distance (adding linear displacement between each consecutive time point), and approximate area (product of 4*SD in the AP and ML directions) of COP movement were calculated. None of the measures had normal distribution so Kruskal-Wallis test with post-hoc Bonferroni correction was used (SPSS 25).

Results: Age was similar between all groups, and disease duration, motor UPDRS and MOCA scores were similar between the PD groups. In quiet stance there was increased variance (p=0.017) and %CV (p=0.032) in COP movement in the AP but not ML directions between FOG and HC. The total quiet stance area (p=0.029), but not AP or ML distance of COP movement was higher in FOG compared to HC. The quiet stance AP COP variance in PD patients was correlated with FOGQ scores (Spearman's coefficient=0.250, p=0.042) but not motor UPDRS or MoCA scores. There were no statistically significant differences between the FOG and noFOG groups.

Conclusion: In our cohort, compared to previous reports, significant differences in AP but not ML postural control in quiet stance were found between PD and HC, but not FOG and noFOG. However, FOGQ scores in quiet stance were correlated with variance of AP COP. Future longitudinal studies are needed to determine if changes in postural sway pre-date development of FOG.

472. Abdominal Wall Dyskinesia

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Introduction: The clinical presentation of repetitive, dyskinetic, and involuntary motions of the anterior abdominal wall was first introduced as "belly dancer's dyskinesia." Etiologies of this rare condition include idiopathic, medication-induced, or post-surgical. We report a case of abdominal and chest wall dyskinesia secondary to prochlorperazine intake.

Case Report: The patient is a 68 year old male who presents with sudden onset involuntary chest and abdominal wall movement. The movement is observed as bilateral, writhing, and continuous, along with classic orobuccolingual stereotypic movements of tardive dyskinesia. In January 2019, the patient began chemotherapy for cardiac amyloidosis, and was also prescribed prochlorperazine (Compro) 5 mg tablets to combat nausea/vomiting. Patient was a somewhat poor historian; he initially reported taking 20 tablets in one day, but then later reported 4-6 tablets per day. After chemotherapy concluded in May, the patient reports continuing prochlorperazine as needed for nausea. Pharmacy records show the patient obtained prochlorperazine from multiple pharmacies, summing up to 1620 obtained tablets over 7 months. The patient reports discontinuing prochlorperazine altogether in August 2019, and the abdominal movements beginning 2 weeks afterward. Acutely, the patient improved on clonazepam 1 mg TID.

Discussion: Upon history and medication review, we suspect the abdominal wall dyskinesia to be an unusual and rare extrapyramidal manifestation of prochlorperazine, termed "belly dancer's dyskinesia". The patient's bloodwork, imaging, physical examination, and medical history were unremarkable and did not reveal other potential causes of dyskinesia. Furthermore, the temporal relationship of drug cessation and symptom onset further raises suspicion of this disorder secondary to medication. Dyskinesia of the abdominal wall has not been previously reported with prochlorperazine use.

Conclusion: Our patient with bilateral, writhing, and continuous abdominal wall movement, accompanied with orobuccolingual stereotypies, has a clinical diagnosis of "belly dancer's dyskinesia" secondary to prochlorperazine intake.

473. The Paradox of The Pianist: A Case Report on the Violation of Fitt's Law in Piano Performance at Different Tempi in a Patient with Cerebellar Tremors

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Background: According to Fitt's Law, as the speed of movement increases, the less accurate and precise the task becomes

(Zhai, Speed-Accuracy Tradeoff in Fitts' Law Tasks, 2004). Given this, it is expected that movement becomes profoundly affected when doing tasks with increasing speed among patients with cerebellar tremors.

Objective: To present a case of a patient diagnosed with cerebellar tremor violating Fitt's Law.

Case Report: A 62-year-old right-handed female who was followed for two years at the clinic due to a constellation of neurologic problems developed a cerebellar tremor with intention and postural features. Her avocation is piano-playing. She noticed that when her tremors were more severe, she is able to accurately play the fast tempo piano pieces such as The Entertainer but she would have mistrokes playing in slower tempo. When the tremor is better, she is able to play slower tempo pieces such as Moonlight Sonata but would have difficulty playing with faster tempo.

Results: *Abnormalities in Neurologic Examination* Mental Status: Oriented x2. Immediate Recall: Digit Span: 2 forwards; 3 backward. Semantic Fluency Test 14 (below normal). Cranial Nerve (CN): CNII: Visual Acuity OD 20/50; OS 20/40 with correction. CN VIII: Calibrated finger rub auditory screening test (CALFRAST): AD Strong, 5cm; AS Strong, 70 cm. CN IX and X: decreased gag reflex bilaterally. Motor: Abductor Pollicis Brevis 3/5 bilaterally. Sensory: Vibration: Rydel-Seiffer Tuning Fork 6 upper extremities, bilateral. 0 lower extremities, bilateral.Cerebellar: Finger to Nose dysmetria, bilateral. Dysdiadochokinesia, bilateral. Positive Holmes Rebound phenomena, bilateral, with Vertical Titubation. Low amplitude, high frequency postural and intention tremors, bilateral upper extremity. Handwriting: Cursive type with Archimedes screw, large with superimposed tremor.Gait: Unstable when walking normally, toe and tandem walking. Poor arm swing in heel walking.

Conclusions: Rapid keystroke playing minimally requires extensor muscle activity making the absence of antagonist movement in cerebellar tremors less noticeable even during more severe tremors. On the other hand, slow keystroke playing requires considerable flexor and extensor muscle activity. Knowledge of the specific muscle activities and the influence of tremors on these suggests the possibility of using activities with variable speed as a means for rehabilitation for patients with tremors.

474. Slower Progression in Double Mutation *GBA-LRRK2*(G2019S) Associated Parkinson Disease

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Background: Interactions of different genetic etiologies are postulated for Parkinson Disease, including a possible milder phenotype of people affected with both *LRRK2* and *GBA* mutations, than *GBA* alone. We combined data from multiple cohorts to assess whether longitudinal motor and cognitive decline in PD patients with both mutations(GBA-LRRK2-PD) differs from participants carrying one(GBA-PD, LRRK2-PD) or neither mutation(Idiopathic PD, IPD).

Methods: Individuals with Parkinson Disease (PD) (n=1,188) from the AJ *LRRK2* Consortium, Parkinson Disease Biomarker Program, Harvard Biomarkers Study (http://www.bwhparkinsoncenter.org/biobank/), SPOT, and Mount Sinai Beth Israel included: IPD(n=910), GBA-PD(n=109), LRRK2-PD(n=155), and GBA-LRRK2 PD(n=14). The rate of change in motor (MDS-UPDRSIII) and cognition (MoCA) was evaluated using linear mixed-effects models using PD duration as the time scale, adjusting for gender, age and PD duration at baseline, levodopa equivalent dose (motor) and cohort.

Results: At baseline, age(p=0.03), PD duration(p<0.001), and gender(p=0.037) were different between IPD (66.5±10.0, 61.0±10.0, 38.7%), GBA-PD(64.8±9.8, 57.6±10.5, 44.0%), LRRK2-PD(68.4±9.2, 60.1±9.6, 50.3%), and GBA-LRRK2-PD(66.2±9.1, 59.0±11.3, 50.0%). Longitudinal follow-up included annual visits (range/yrs:0-12). The estimated rates of MDS-UPDRSIII worsening(points/year) were: GBA-PD=1.27±0.27, IPD=0.88±0.16, LRRK2-PD=0.60±0.21, and GBA-LRRK2-PD=0.46±0.37. Harboring a *LRRK2*-G2019S mutation was associated with slower motor deterioration whether or not also carrying a *GBA* mutation(difference: GBA-LRRK2-PD vs GBA-PD=-0.80±0.39, p=0.04; LRRK2-PD vs IPD=-0.28±0.19, p=0.15), though not significant in absence of *GBA*. While *GBA* mutations were marginally associated with faster deterioration among non-*LRRK2*-G2019S carriers(GBA-PD vs IPD: 0.38±0.25, p=0.12), its effect among *LRRK2*-G2019S carriers(GBA-LRRK2-PD vs LRRK2-PD: -0.14±0.36, p=0.70) diminished. The estimated rates of decline(points/year) in total MoCA score were: GBA-PD=-0.55±0.09, IPD=-0.29±0.05, LRRK2-PD=-0.19± 0.06 and GBA-LRRK2-PD=-0.16± 0.06. Among non-*LRRK2*-G2019S carriers, carrying a *GBA* mutation was associated with faster cognitive decline(GBA-PD vs IPD: -0.26±0.08, p=0.002), but the effect diminished among *LRRK2*-G2019S carriers(GBA-LRRK2-PD vs LRRK2-PD: -0.04±0.068, p=0.59). *LRRK2*-G2019S mutations were associated with slower cognitive decline among *GBA* carriers(GBA-LRRK2-PD vs GBA-PD: 0.36±0.09, p<.001), while in a lesser magnitude in absence of *GBA* (LRRK2-PD vs IPD: 0.09±0.06, p=0.09). The interaction effect between *LRRK2*-G2019S and *GBA* mutations was

significant(estimate=0.30±0.11, p=0.006), with the effect of *LRRK2*-G2019S mutations intensified and the effect of *GBA* mutations weakened in presence of each other.

Discussion: This longitudinal study provides further evidence that there is an interaction between *GBA* and *LRRK2* mutations, particularly with regard to cognitive phenotypes, with *LRRK2* dominating *GBA* mutations. Further study, including assessing biomarkers in those with mutations in both genes and mutation type is warranted to better understand these interactions and potential therapeutic implications.

475. Long-Term Goal Achievement and Satisfaction after Deep Brain Stimulation in Parkinson's Disease

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Background: Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) is a successful treatment providing both short and long-term motor improvement in Parkinson's disease. However, failure to achieve patient expectations could result in overall dissatisfaction despite significant motor improvement. Research in long-term satisfaction after STN-DBS remains limited, and the important factors that affect satisfaction are not fully understood.

Objective: To evaluate the relationship between long-term satisfaction and patient goal achievement along with other standard DBS outcome measures in Parkinson's disease patients undergoing Subthalamic Nucleus Deep Brain Stimulation (STN-DBS).

Method: Fifty-seven patients who underwent bilateral STN-DBS were asked to recall three pre-surgical goals, to rate the degree of goal achievement, and to report the overall satisfaction five years after surgery. We examined patient-selected goals and subjective goal achievement to investigate the relationship between goals and satisfaction in STN-DBS. Additionally, we studied the relationship between patient satisfaction and the standard DBS outcome measures, such as Unified Parkinson Disease Rating Scale (UPDRS), Activities of Daily Living (ADL), and Mini Mental State Exam (MMSE).

Results: The three most frequently selected goals were "dyskinesia" (39 of 57), "tremor" (37 of 57), and "gait disorder" (35 of 57). Of the patients who selected the goal, the percentage of patients who achieved the goal for "dyskinesia" was 94.9%, for "tremor" was 91.9%, and for "gait disorder" was 77.1%. A strong correlation exists between long-term satisfaction and goal achievement ($r=0.757$; $p<0.001$). In addition to goal achievement, post-operative motor and ADL scores correlated with long-term patient satisfaction. Only the post-operative mental component of SF-36 correlated with satisfaction, whereas the physical component of SF-36 did not.

Conclusion: Important factors influencing long-term patient satisfaction after STN-DBS were patient goal achievement, motor outcome, and ADL. Assessing patient's subjective goal achievement, in addition to the standard clinical measures, is important in providing long-term satisfaction after STN-DBS.

476. Comparing Rates of Motor Progression before and after DBS among Patients with Idiopathic and LRRK2-Associated Parkinson's Disease

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Objective: To systematically assess the rate of motor progression among patients with idiopathic and Leucine Rich Repeat Kinase 2 (LRRK2)-associated Parkinson's Disease (PD) both before and after deep brain stimulation (DBS) surgery.

Background: Previous studies have suggested that the progression of motor symptoms is often slower in patients with LRRK2-associated PD than in those with idiopathic forms (iPD) of the disease. It has also been shown in small studies with limited long-term follow up that patients with LRRK2-associated PD have improved motor outcomes compared to iPD following DBS. To date, however, there have been no formal analyses of the potentially differential rates of motor progression before and after DBS between these two groups.

Methods: Fourteen subjects with iPD and nine with LRRK2-PD with available longitudinal data were identified at Mount Sinai Beth Israel Medical Center between July 2009 and July 2017. Patients with glucocerebrosidase mutations were excluded. Demographic and clinical information was collected including age at PD onset, site of primary symptoms, duration of disease, surgical date, brain target, each study visit, Unified Parkinson's Disease Rating Scale motor subscale (UPDRS-III), and levodopa equivalent daily dose (LEDD). Linear mixed models adjusted by gender, age of onset, LEDD, age at surgery or at baseline visit, and baseline UPDRS-III were used to compare the rate of change of UPDRS-III scores both before and after surgery between the two groups.

Results: For patients with iPD, there was an average increase of 0.03 UPDRS-III points per month before surgery (95%CI: -0.09,0.16) and 0.11 points per day following surgery (95%CI: 0.07, 0.15). Compared to patients with LRRK2-associated PD, these rates represent a differential rate of 0.10 points/month (95%CI: -0.16,0.36, p-value=0.76) before surgery, with LRRK2-PD patients worsening faster before surgery, and a differential rate of 0.07 points/month (95%CI: -0.16, 0.02, p-value=0.15) following surgery, with LRRK2-PD patients worsening more slowly.

Conclusions: Our study supports previous findings on the favorable postoperative course of LRRK2-PD. The post-operative course appeared to be steeper for iPD. However, this result did not reach significance and our wide confidence intervals preclude confident interpretations. Knowledge of the longitudinal course may inform optimal patient selection for DBS.

477. Effect of Opicapone and Entacapone on Early Morning-OFF Pattern in Parkinson's Disease Patients with Motor Fluctuations

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Background: Opicapone is a once-daily catechol-O-methyltransferase inhibitor, which has shown to be effective for end-of-dose motor fluctuations in Parkinson's disease (PD) patients in two large multinational trials (BIPARK-I [Ferreira, *Lancet Neurol*, 2016] and BIPARK-II [Lees, *JAMA Neurol*, 2017]). BIPARK-1 diary data were analyzed post hoc to evaluate the effects of opicapone 50 mg versus entacapone on early morning-OFF (EMO) patterns.

Methods: Home-diary data from patients with wearing-OFF treated with opicapone 50 mg or entacapone in the BIPARK-I trial were analyzed. Patients' 24-h diary data were stratified per daily hour. Asleep and ON/OFF fluctuations were characterized and depicted by daily hour. Proportion of patients who woke up in ON-/OFF-status and time-to-ON from first morning levodopa intake after wake-up were analyzed after a continuous period of >/=4 hours of sleep. EMO pattern was defined as the morning period for which %/h asleep-time was (1) not negligible (<5%/h), (2) <50%/h and (3) <%/h OFF-time.

Results: A total of 235 patients were included in the analysis. For both treatments, at baseline and endpoint, the majority of asleep-time (>50%/h) was within 11pm to 6am and the proportions of patients taking levodopa per daily-hour were comparable. Asleep-time was considered negligible (<5%/h) from 9am to 9pm. At baseline, <15% of patients woke up in ON-status, time-to-ON was >1h and EMO pattern was found to be between 6am to 8am. At endpoint, for opicapone 50 mg, the proportion of patients who woke up in ON-status increased by 12.2% from baseline, in comparison with 7.5% for entacapone. For patients treated with opicapone 50 mg, time-to-ON decreased by 17.7%, in comparison with 1.9% for entacapone. As reduction of morning OFF-time (%/h) was two-fold greater for opicapone 50 mg versus entacapone (20% vs 10%), no EMO was observed for opicapone 50 mg, but EMO was still observed for entacapone.

Conclusions: Treatment with opicapone 50 mg, in comparison with entacapone, led to a greater increase in the proportion of patients who woke up in ON-status and a greater decrease in time-to-ON from first morning levodopa intake. In addition, due to a substantial reduction in morning OFF-time, no EMO pattern was found for patients treated with opicapone, in contrast to entacapone.

478. Exploring Populations for Intervention at an Urban VA Medical Center

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Objective: Review the diversity of patient populations at an urban Veterans Affairs (VA) Consortium center to target most relevant future interventions and studies.

Background: VA patients may have more comorbidities that lead to more varied patterns of movement disorder diagnoses, for whom the standard array of clinical trials may not apply.

Methods: Chart review was performed for patients seen at the Jesse Brawn VA (JBVA) Movement Disorders clinic between July 2009 and April 2020.

Results: 668 Veterans were evaluated, mean age was 70.7 (12.4), range 26-98, 27.5% had died since 2009. 57.5% were Vietnam veterans and 18.6% were from the Korean War era. 52.4% were Caucasian, 41.2% African American, 5.5% Hispanic/Latino. 96% were male. Most common diagnosis was Parkinson's Disease (PD) (26.2%) followed by ET (14.7%). Other causes of parkinsonism (atypical, drug, secondary) totaled 26.5%. Functional movement disorders were seen in 5.4%. Rare or unusual diagnoses were only seen in a minority of cases. 9.9% of the patients were treated with botulinum toxin (BTX) and only 2.7% received deep brain stimulation (DBS).

Conclusion: With a large contingency of racial minorities, JBVA may be a good location to explore racial disparities in care, particularly in regards to advanced treatments such as BTX and DBS, which were applied in a fraction of patients. Only a small portion of the patients had probable PD, with a broad diversity of other causes of parkinsonism, making traditional PD trials less fruitful in this population. ET (usually severe) is commonly represented and may be a targeted area of intervention, as are disabling functional movement disorders, seen at a similar frequency to specialty tertiary centers.

479. Istradefylline, an Adenosine A_{2A} Receptor Antagonist, as Adjunct to Levodopa in Parkinson's Disease (PD): A Pooled Safety Analysis of 4 Randomized Controlled Trials

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Introduction: Istradefylline, a selective adenosine A_{2A} receptor antagonist that acts via the indirect basal ganglia outflow pathway, is indicated in the US as adjunctive treatment to carbidopa/levodopa in adults with PD experiencing OFF episodes. This pooled analysis evaluated the safety of istradefylline plus levodopa in patients with PD experiencing motor fluctuations from the 4 trials that constituted the basis for the FDA's approval of istradefylline.

Methods: Safety was evaluated in 4 randomized, double-blind, placebo-controlled, 12-week phase 2b/3 studies, in which patients received istradefylline (20 or 40 mg/day) or placebo. Patients continued treatment with carbidopa/levodopa and other adjunctive anti-PD medications they may have been taking with no changes from pre-study doses. Treatment-emergent adverse events (TEAEs) were recorded throughout.

Results: The safety analysis set comprised 1160 patients (20 mg/day, n=356; 40 mg/day, n=378; placebo, n=426). TEAEs occurred in 67.7% on 20 mg/day and 69.6% on 40 mg/day istradefylline and in 65.3% on placebo. Treatment-related TEAEs occurred in 42.7% of patients receiving 20 mg/day istradefylline, 47.4% receiving 40 mg/day, and 40.4% receiving placebo. The most common TEAE was dyskinesia (20 mg/day, 14.6%; 40 mg/day, 16.7%; placebo, 7.5%). Other TEAEs occurring in >5% of patients in either istradefylline-treated group were viral upper respiratory infection, nausea, dizziness, constipation, and insomnia. The rate of discontinuation due to TEAEs was similar between the istradefylline-treated groups (20 mg/day, 5.1%; 40 mg/day, 6.1%) and placebo (4.5%). Discontinuation due to dyskinesia was 1% in both istradefylline treatment arms (placebo, 0%). Serious adverse events (SAEs) occurred in 3.7% of patients receiving 20 mg/day istradefylline, 5.8% receiving 40 mg/day, and 2.6% receiving placebo and were treatment-related in 1.4%, 1.9%, and 1.2% of patients, respectively. TEAEs of special interest included falls (20 mg/day, 6.5%; 40 mg/day, 6.9%; placebo, 9.4%), halluicination (2.2%, 5.8%, 2.8%), impulse control disorder (0, 0.3%, 0), increased liver enzymes (0.8%, 1.9%, 2.6%), nausea and vomiting (4.8%, 6.9%, 4.7%), neutropenia (0.3%, 0.5%, 0), orthostatic hypotension (6.7%, 6.9%, 5.4%), and sleep disturbance (0.8%, 1.6%, 0.7%).

Conclusions: In this pooled analysis of 4 studies, istradefylline, a nondopaminergic A_{2A} receptor antagonist, had an acceptable safety profile when administered adjunctively to carbidopa/levodopa with or without other anti-PD medications in PD patients with OFF episodes.

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480. Relationship of Cerebrospinal Fluid Vitamin B12 Status Markers with Parkinson's Disease Progression

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Background: Using stored blood specimens from untreated, early Parkinson's disease (PD) patients from the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial, we found that subjects in the low serum vitamin B12 tertile experienced greater (worse) annualized change in ambulatory capacity score compared with those in the other tertiles, while those with moderately elevated (>15μmol/L) total homocysteine (tHcy) had greater annualized declines in the Mini-Mental Status Exam (MMSE).

Objectives: To determine whether levels of cerebrospinal fluid (CSF) B12 analytes were also associated with progression of PD.

Methods: We measured B12, holotranscobalamin (holoTC), methylmalonic acid(MMA), and tHcy in 581 CSF samples obtained at the baseline visit of the DATATOP study.

Results: The geometric mean(± SD) for CSF B12 was 17.3pmol/L(±7.2), for holoTC was 15.5pmol/L(±9.4), for MMA was 0.34μmol/L(±3.9), and for tHcy was 58.7nmol/L (±43.7). CSF B12 and holoTC were strongly correlated, r= 0.87, p<.001. While there was a trend for greater annualized worsening of the ambulatory capacity score in the low CSF B12 tertile, this was not significantly different. However, the annualized change in the UPDRS "walking" item was worse in the low B12 tertile. No association with change in MMSE was seen for those 7% with the highest baseline CSF tHcy.

Conclusions: In these early, untreated PD subjects, low CSF B12 predicted greater worsening of the UPDRS "walking" item, while CSF tHcy was not associated with progression of cognitive impairment. These findings in CSF B12 and holoTC extend and partially support our findings in serum.

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481. Nilotinib Increases Brain Dopamine and Lowers CSF Tau and Oligomeric Alpha-Synuclein in Parkinson's Disease

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This is a single center phase II, randomized, double-blind, placebo-controlled study to evaluate the effects of nilotinib, a potentially disease modifying drug in Parkinson's disease (PD). Our preclinical evidence indicate that nilotinib increases brain dopamine levels and reduces toxic tau and alpha-Synuclein via autophagy in models of neurodegeneration. We predicted that nilotinib alters exploratory biomarkers via inhibition of Abl in the CSF after 12-month daily nilotinib treatment in 3 groups, including placebo (n=21), 150mg nilotinib (n=21) and 300mg nilotinib (n=20). We did not detect any plasma or CSF Abl inhibition. The 150 mg nilotinib group shows an increase in dopamine metabolites homovanillic acid (159.80nM, 90% CI, 7.04-312.60, p=.04) and 3.4-Dihydroxyphenylacetic acid (4.87nM, 90% CI 1.51-8.23, p=.01) and the 300 mg nilotinib group shows an increase in 3-4-Dihydroxyphenylacetic acid (7.52nM, 90% CI 2.35-12.69, p=.01). The 150 mg nilotinib but not the 300 mg group shows reduction of alpha-synuclein oligomers (-0.04pg/ml, 90% CI -0.08- -0.01, p=.03). A significant reduction of hyper-phosphorylated tau is seen in the 150 mg nilotinib (-10.04pg/ml, 90% CI -17.41- -2.67, p=.01) and the 300 mg nilotinib (-12.05pg/ml, 90% CI -19.21- -4.90,

p=.01) groups. This study met its objectives that nilotinib robustly alters CSF dopamine metabolism and misfolded proteins, independent of Abl inhibition. Taken together, our data will guide the development of a phase III study to investigate the effects of nilotinib using dopamine metabolites as biomarkers in response to nilotinib in PD.

482. A Pooled Analysis of Four Pivotal Randomized Controlled Trials of Istradefylline, an Adenosine A_{2A} Receptor Antagonist: Efficacy as Adjunct to Levodopa in Parkinson's Disease (PD)

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Background: Istradefylline, a selective adenosine A_{2A} receptor antagonist that acts via the indirect basal ganglia outflow pathway, is indicated in the US as adjunctive treatment to levodopa/carbidopa in adults with PD experiencing OFF episodes. Four 12-week, randomized, double-blind, placebo-controlled, parallel-group clinical trials were the basis for istradefylline's FDA approval. The objective of this analysis was to report the pooled efficacy results for istradefylline in these 4 pivotal studies of levodopa-treated patients with PD experiencing motor fluctuations.

Methods: Istradefylline was evaluated in patients with PD receiving levodopa with carbidopa or benserazide and having motor fluctuations. All patients could continue other baseline anti-PD medications at pre-study doses. Change in daily OFF time at Week 12 as recorded in patient-completed 24-hour ON/OFF diaries was the primary endpoint. All studies were designed to have common methodology to facilitate pooling of results. Pooled analyses of once-daily oral istradefylline (20 and 40mg/day) and placebo were evaluated using a mixed-model repeated-measures approach (with study as a factor).

Results: The pooled analysis included 1143 patients (placebo, n=420; 20mg/day, n=347; 40mg/day, n=376). At Week 12, OFF hours/day with 20 and 40mg/day istradefylline were reduced from baseline more than with placebo (least-squares mean difference [LSMD] [95%CI] -0.75 [-1.10, -0.40] and -0.82 [-1.17, -0.47], respectively). ON hours/day without troublesome dyskinesia (ON-WOTD) increased from baseline with istradefylline compared with placebo (LSMD vs placebo in change from baseline, 20mg/day, 0.68 [0.31, 1.06]; 40mg/day, 0.69 [0.32, 1.07]). Change from baseline in asleep hours/day was not significantly different between istradefylline and placebo (LSMD vs placebo in change from baseline, 20mg/day, -0.07 [-0.23, 0.10]; 40mg/day, -0.04 [-0.20, 0.13]). ON hours/day with troublesome dyskinesia (ON-WTD) did not increase with istradefylline vs placebo (LSMD vs placebo in change from baseline, 20mg/day, 0.13 [-0.07, 0.32]; 40mg/day, 0.15 [-0.05, 0.34]). Istradefylline was generally well tolerated; the completion rate across the 4 studies was 88-90%. Dyskinesia was the most frequent adverse event (20mg/day, 15%; 40mg/day, 17%; placebo, 8%).

Conclusions: This pooled analysis illustrates that for patients with PD experiencing levodopa-mediated motor fluctuations, istradefylline 20 and 40mg/day significantly improved OFF time and ON-WOTD with little effect on time asleep or ON-WTD.

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483. Safety and Pharmacokinetics of ATH434 (PBT434), a Novel Small Molecule Inhibitor of α-Synuclein Aggregation, in Adult and Older Adult Volunteers

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Objective: Evaluate the safety, tolerability, cardiac repolarization, and pharmacokinetics of ATH434.

Background: ATH434 is a novel, brain penetrant small molecule inhibitor of α-synuclein aggregation. In transgenic mouse models of Parkinson disease (PD;A53T) and Multiple System Atrophy (MSA;PLP-α-Syn), ATH434 reduced α-synuclein aggregation and markers of oxidative stress, preserved neurons, and improved motor function. ATH434 reduced glial cell inclusions (PLP-α-Syn). ATH434 is thought to act by redistributing labile iron across neuronal membranes. The affinity of ATH434 for iron is lower than for iron trafficking proteins, such as transferrin and ferritin.

Design/Methods: In this randomized, double-blind, placebo-controlled study, adult subjects received single oral doses (8/cohort) at 50, 100, 300 or 600 mg or 8 days dosing (10/cohort) at 100, 200 or 250 mg bid. Older adults (≥65 years) received 250 mg bid for 8 days. Serial blood samples were collected post-dose and CSF was sampled at 1.5 or 11 hours post-dose at 200-250 mg bid at steady state. Safety was assessed with physical examination, adverse events (AEs), laboratory tests and 12-lead ECGs. A concentration-effect analysis was performed to estimate the effect of ATH434 on the QT interval using ATH434 plasma levels and ECGs extracted from continuous Holter monitoring at pre-specified timepoints.

Results: ATH434 was readily absorbed with a T_{max} of 0.5-2 hours and demonstrated dose-dependent pharmacokinetics after single and multiple doses. Mean elimination half-life up to 9.3 hours was observed independent of dose. CSF concentrations near T_{max} were 102.5 to 229.5 ng/mL, comparable to free ATH434 concentrations in plasma. AE rates were similar for ATH434 and placebo. All AEs were mild to moderate in severity. There were no serious AEs or AEs leading to discontinuation. The AE profile was similar for adult and ≥65 year-old volunteers. There were no clinically significant vital sign, laboratory or 12-lead ECG findings. A linear mixed-effects model predicted the placebo-corrected, baseline-adjusted change in QTcF to be <2 ms (upper bound of 90%CI <4 ms) at the anticipated steady state C_{max}.

Conclusions: ATH434 is an orally bioavailable, brain penetrant, small molecule inhibitor of α-synuclein aggregation. CSF concentrations at doses ≥200 mg bid were greater than

those associated with efficacy in animal models of PD and MSA. ATH434 was safe and well tolerated at all doses and has no evidence of cardiac liability.

484. Nilotinib is Reasonably Safe and May Halt the Disease Progression in Moderately Severe Parkinson's Disease Patients

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This is a phase II, randomized, double-blind placebo-controlled trial to evaluate the effects of a potential disease modifying drug in PD. The primary objective was nilotinib safety and tolerability in moderately severe PD patients. An exploratory objective is to assess nilotinib effects on motor and non-motor symptoms at baseline, 6, 12 and 15 months. Participants were confirmed to have PD according to the UK Brain Bank diagnostic criteria, with Hoehn and Yahr stage 2.5-3, MDS-UPDRS-III motor score 20-40 and MoCA ≥22. 75 participants were randomized 1:1:1 into placebo, 150mg and 300mg nilotinib oral, once daily for 12 months. A total of 100 participants were screened, 25 did not meet the inclusion criteria due to QTc prolongation. Participants were on average 68.4 years of age and included 20 females and 55 males. 88% of participants completed the treatment and there were no drop-outs due to lack of drug tolerability. Niltonib was found to be reasonably safe with no suspected drug related adverse effects. There was no QTc prolongation or myelosuppression. No differences were observed in MDS-UPDRS-I within and between all study groups tested by a single rater. All groups showed a significant decline in MDS-UPDRS-II scores between baseline and 12 months and after washout. All groups slightly improved on MDS-UPDRS-III motor between baseline and 6 months. The placebo and the 300 mg nilotinib groups remained stable at 12 months and after washout but there was a significant improvement in MDS-UPDRS-III score between baseline and 15 months in the 150 mg nilotinib group (-2.82 points, 95% CI, -4.75--0.89). No significant differences were observed in MDS-UPDRS-IV. No statistically significant differences in MDS-UPDRS measurements were observed between groups. There were no statistically significant differences in PDQ-39 between groups, but the placebo group significantly deteriorated after 6 months, while the nilotinib groups did not change. In conclusion this exploratory measures show no clinical worsening in UPDRS in the nilotinib groups compared to the placebo group that worsened after 6 months of treatment. Taken together, our results will guide the future development of a definitive phase III study to evaluate the effects of nilotinib in PD.

485. Onset of Drug-Related Adverse Events in Parkinson's Disease Patients with Motor Fluctuations Treated with Opicapone in Clinical Practice: OPTIPARK Post-Hoc Analysis

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Background: Opicapone proved to be effective in treating end-of-dose motor fluctuations in Parkinson's Disease (PD) patients in two large clinical trials [Ferreira, *Lancet Neurol*. 2016, Lees, *JAMA Neurol*. 2017]. The OPTIPARK study evaluated opicapone 50 mg in a heterogeneous population of PD patients treated in clinical practice.

Methods: OPTIPARK was a prospective, open-label, single-arm, multicentre trial conducted in Germany (3 months) and the UK (6 months) under clinical practice conditions. PD patients with motor fluctuations received opicapone 50 mg in addition to current antiparkinsonian treatment. Safety assessments included evaluation of treatment-emergent adverse events (TEAEs). This *post-hoc* analysis investigated the onset of TEAEs that were considered at least possibly related to opicapone treatment.

Results: Of the 506 patients enrolled, 495 patients took at least 1 dose of opicapone (Safety set), 63.6% were male, with a mean age of 67.7 years. TEAEs considered at least possibly drug-related to opicapone were reported for 45.1% of patients, with dyskinesia (11.5%) and dry mouth (6.5%) being the most frequently reported. The majority of at least possibly drug-related TEAEs were reported during the first week of opicapone treatment, and from the third week onwards the incidence of these TEAEs was consistently low (<4%). Within the first week of opicapone treatment, dyskinesia was the most frequently reported at least possibly drug-related TEAE (6.5%) but with very low impact on patient discontinuation (<0.5%).

Conclusion: In the OPTIPARK study, most TEAEs considered at least possibly drug-related had fast onset within the first week of opicapone 50 mg treatment followed by consistently low incidence for 6 months. These observations are relevant for patient management in clinical practice.

486. Parkinson Disease Symptoms and the Company They Keep as Reported Directly by 21,649 Patients

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Background: There has been no systematic research to characterize neurological disease as reported directly by patients. The Parkinson Disease Patient Report of Problems (PD-

PROP) captures, by keyboard entry, the prioritized, verbatim accounts from consenting PD patients about what bothers them the most about their PD and in what way this problem affects their daily functioning.

Methods: For baseline reports accrued on the FoxInsight.org research platform as of July 2019, natural language processing (NLP), n-gram extraction, expert clinical curation of symptom and sub-symptom categories, and machine learning were used to analyze the verbatim keyboard-entered text of the highest prioritized bothersome symptoms. The company the symptoms keep was analyzed employing Euler and UpSet plots in ShinyApps.io.

Results: A total of 21,649 unique patient reports yielded categories of four most bothersome motor (55.1%) (Tremor, Rigidity, Bradykinesia, Postural Instability), six most bothersome non-motor problems (37.6%), (Cognition, Sleep, Fatigue, Mood, Pain, Autonomic Dysfunction), and as-yet unclassified (7.3%) most bothersome problems. Tremor (48.5%) and Postural Instability (45.4%) were the most frequently reported motor problems, and Cognition (26.3%) was the most frequently reported non-motor problem. When reports of PI and Cognition co-occurrence were examined, these two categories collectively constituted 37.2% of the overall problems for the group within one year since diagnosis (YSD) of PD and similarly 37.8% for 0-3 YSD, overlapping by about 8% for both YSD groups. Major associated Postural Instability symptom categories of gait disorder, balance, and falling were reported as both isolated and overlapping problems, while major associated Cognition categories of word finding, memory, and concentration were largely reported as isolated problems.

Conclusions: After Tremor, symptoms of Postural Instability and Cognition, the most therapeutically intractable features of PD, predominated in patient reports of their most bothersome problems. The PD-PROP can identify patient-reported symptoms and may be useful in ascertaining clinical trial participants based on their verbatim-reported and clinically curated bothersome problems.

487. The Utility of [^{123}I] Ioflupane Spect Imaging in African-American Patients: A Retrospective Chart Review Study

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Background: Parkinson disease (PD) is more common in Caucasians than in African-Americans, although a biological basis of this racial difference remains unknown. Dopamine transporter (DAT)-SPECT imaging has been widely used to assess presynaptic dopaminergic function. However, the utility of DAT-SPECT in African-American patients has not been well studied.

Objectives: To explore if racial differences exist in [^{123}I] ioflupane DAT binding between African-Americans and Caucasians with presynaptic dopaminergic deficiency.

Methods: Retrospective chart review was conducted for 229 consecutive patients with [^{123}I] ioflupane SPECT imaging performed in a single academic medical center. All image studies were visually inspected by a certified Radiologist (V-V) and interpreted as with normal (n=130) or abnormal (n=99) presynaptic dopaminergic function. Quantitative [^{123}I] ioflupane uptake as measured by striatal binding ratios (SBR) computed by DaTQUANT software were available in 173 of the 229 patients, including 112 Caucasians and 58 African-Americans. SBRs of right and left striatum and its sub-regions (caudate, anterior putamen and posterior putamen) were compared between African-American and Caucasian patients with normal and abnormal presynaptic dopaminergic function.

Results: Among the 104 out of 173 patients with normal presynaptic dopaminergic function, no statistical difference was detected in SBRs of all analyzed striatum regions between African-Americans (n=36, mean age 66.5, 39% female) and Caucasians (n=68, mean age 68.4, 41% female). In patients with abnormal presynaptic dopaminergic function, African-Americans (n=22, mean age 67.0, 32% female) appeared to have less reduction of [^{123}I]ioflupane uptake as measured by SBRs in left striatum (p=0.02), left anterior putamen (p=0.02), right posterior putamen (p=0.04), and left posterior putamen (p=0.03) compared to Caucasians (n=44, mean age 67.0, 30% female). When only patients with clinical diagnosis of PD after post-scan follow-up were analyzed, similar statistically significant less reduction of [^{123}I]ioflupane uptake in left striatum, left anterior putamen, and bilateral posterior putamens was observed in African-Americans (n=16, mean age 66.4, 31% female; mean disease duration 3.75 years; mean follow-up time 21.9 months) compared to Caucasians (n=27, mean age 64.7, 22% female; mean disease duration 3.76 years; mean follow-up time 23.4 months).

Conclusions: In this retrospective study, we observed racial differences of [^{123}I]ioflupane DAT binding among African-Americans with presynaptic dopaminergic deficit Parkinsonian Syndrome (PD in particular). Future large sample studies are needed to further investigate if racial differences exist in patients with presynaptic dopaminergic dysfunction and its underlying mechanism in different ethnic groups.

488. Safety and Tolerability of Bone Marrow-Derived Allogeneic Mesenchymal Stem Cells in Parkinson's Disease Patients

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Objective: Prove the safety and feasibility of delivering allogeneic bone marrow-derived mesenchymal stem cells (MSC) intravenously in escalated doses to patients with idiopathic Parkinson's disease (PD).

Background: Neuroinflammation plays a crucial role in the pathogenesis of PD, supporting the rationale for using MSC as immunomodulatory therapy for restoring homeostasis to the neuronal-glial microenvironment.

Methods: 12-month single-center open-label dose-escalation phase 1 study. 20 subjects with mild/moderate PD were recruited from a larger screening pool of 152 and sequentially assigned to one of four doses: 1, 3, 6, or 10 X 10^6 MSCs/kg, given a single intravenous infusion following a staggering design and subsequently evaluated at 3, 12, 24, and 52 weeks. Primary outcome safety measures were the absence of immediate transfusion reaction, study-related adverse events, organ damage, or immunogenic responses. Secondary outcomes were therapy's impact on peripheral markers, PD progression, and changes in brain perfusion.

Results: Twenty subjects received a single IV infusion; during the first 24 hours post-infusion, three patients reported transient treatment-emergent adverse events (TEAEs), one phlebitis, one antecubital fossa hematoma, and one headache. Most common TEAEs during the study were dyskinesias (20%, N=4) and hypertension (20%, N=4). One SAE happened in a patient with a 4-year history of lymphocytosis who developed asymptomatic chronic lymphocytic leukemia. There was no response to donor HLA over the 12-month study. At 52 weeks, peripheral markers had a significant change compared with baseline in the highest dose group of 10 x 10^6 MSCs/kg , TNF-α decreased 54 % ($p<0.05$), CCL22 declined 36% ($p<0.05$), along with an increase in BDNF 50 % ($p<0.05$). The highest dose also had the most significant effect on reducing OFF UPDRS motor -14.4 ($p<0.01$) and total scores (-20.8, $p<0.001$). Main effects on brain perfusion occurred with a significant increase in the subthalamic nucleus ($p<0.05$) at 24 weeks.

Conclusions: This study demonstrates that a single infusion of allogeneic MSCs is safe and well-tolerated in mild/moderate PD patients. Further placebo-controlled studies are warranted to explore the mechanism of action and to corroborate the efficacy of MSCs in PD.

489. Long-Term Efficacy of Opicapone in the Reduction of On-Time with Troublesome Dyskinesia in Parkinson's Disease Patients with Motor Fluctuations and Reporting Troublesome Dyskinesia

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Objective: To evaluate the evolution of ON-time with troublesome dyskinesia ('Bad ON-time') following opicapone (OPC) long-term exposure in Parkinson's disease (PD) patients with motor fluctuations and reporting troublesome dyskinesia.

Background: OPC, a once-daily catechol-O-methyltransferase inhibitor, was shown to be effective for end-of-dose motor fluctuations in PD patients in two large multinational trials [1, 2].

Methods: Matching efficacy data from BIPARK-I and II [1, 2] were combined for OPC 50 mg. The studies had similar designs, eligibility criteria and methodologies. Primary efficacy endpoint was change from baseline in OFF-time based on patient diaries. This *post-hoc* analysis was performed to evaluate the long-term effect of OPC on 'Bad ON-time' in patients randomized to OPC 50 mg and already reporting troublesome dyskinesia at baseline, based on patient diaries.

Results: A total of 216 patients were included in the Full Analysis Set. Of these, 44 (20.4%) patients reported ~2 h of 'Bad ON-time' and ~9 h of ON-time without or with non-troublesome dyskinesia ('Good ON-time') at baseline. Following initiation with OPC 50 mg and up to the end of the double-blind period (i.e. after ~3.5 months), an increase of ~1.4 h in 'Good ON-time' and decrease of ~5 mins in 'Bad ON-time' were observed, with an overall mean levodopa reduction of ~40 mg/day. By the end of the 1-year open-label extension (OLE) period, mean daily 'Good ON-time' had increased by approximately 2 h (119.4 min), from 532.8 min at double-blind baseline to 652.2 min at end of OLE, and mean daily 'Bad ON-time' had decreased by approximately 1 h (55.1 min) from 119.6 min at double-blind baseline to 64.5 min at end of OLE. During this time, mean daily levodopa dose decreased by an additional 60 mg, ending in a total decrease of 100 mg, from 740 mg at double-blind baseline to 640 mg at end of OLE.

Conclusions: In PD patients with motor fluctuations and reporting troublesome dyskinesia, treatment with OPC did not exacerbate troublesome dyskinesia; in fact, long-term OPC exposure, associated with a reduction in levodopa dose, led to a relevant reduction of ON-time with troublesome dyskinesia and an increase by approximately 2 h of 'Good ON-time'.

References: 1. Ferreira JJ, et al. Lancet Neurol. 2016;15:154-65. 2. Lees AJ, et al. JAMA Neurol. 2017;74:197-206.

490. Efficacy of Opicapone at Different Levodopa Regimens up to a Threshold of 600mg/Day Levodopa in Parkinson's Disease Patients with Motor Fluctuations

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Objective: To evaluate the efficacy of opicapone (OPC) in Parkinson's disease (PD) patients with motor fluctuations being treated with different levodopa regimens up to a threshold of 600 mg/day levodopa.

Background: OPC, a once-daily catechol-O-methyltransferase inhibitor, was effective for end-of-dose motor

fluctuations in PD patients in two large multinational trials [1, 2].

Methods: Matching efficacy data from BIPARK-I and II [1, 2] were combined for the placebo (PLC) and OPC 50 mg groups. The studies had similar designs, eligibility criteria and methodologies. Primary efficacy endpoint was change from baseline in OFF-time based on patient diaries. Subgroup analyses were performed to evaluate the efficacy of OPC 50 mg in different levodopa regimens up to a threshold of 600 mg/day levodopa (300-400, 400-500 and 500-600 mg/day).

Results: 239 patients were included in the Full Analysis Set (patients treated with >/=1 dose and with >/=1 post-baseline OFF-time assessment; PLC, n=118; OPC 50 mg, n=121). Mean (±standard error) number of levodopa daily intakes was 3.7±0.1 for both PLC and OPC 50 mg with levodopa 300-400 mg/day, 4.3±0.1 and 4.4±0.1 for PLC and OPC 50 mg, respectively, with levodopa 400-500 mg/day, and 4.5±0.1 and 4.3±0.1 for PLC and OPC 50 mg, respectively, with levodopa 500-600 mg/day. Mean OFF-time reduction was at least two-fold greater than PLC when OPC 50 mg was added to any levodopa regimen: mean (95% confidence interval) changes from baseline in absolute OFF-time for OPC 50 mg versus PLC were -102.2 (-138.1, -66.3) versus -53.4 (-89.6, -17.3) min for patients treated with levodopa 300-400 mg/day, -110.0 (-146.7, -73.3) versus -37.2 (-77.7, 3.3) min for patients treated with levodopa 400-500 mg/day, and -117.6 (-152.6, -82.6) versus -23.1 (-67.8, 21.6) min for patients treated with levodopa 500-600 mg/day. It was notable that, with increasing levodopa dose regimens, there was a trend towards decreasing magnitude of effect in the PLC group, compared with a trend towards a slight increase in magnitude of effect in the OPC 50 mg group.

Conclusions: OPC 50 mg showed a similar magnitude of effect between different low levodopa dose regimens, with at least a two-fold greater OFF-time reduction than placebo.

References: 1. Ferreira JJ, et al. Lancet Neurol. 2016;15:154-65. 2. Lees AJ, et al. JAMA Neurol. 2017;74:197-206.

491. Coincidental POLG Mutation Found in a Case of Drug-Induced Parkinsonism

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Background: POLG related disorders constitute a sequence of overlying phenotypes that can present anytime from early infancy to late adulthood.

Literature search and results: We illustrate a case of an 84-year-old man who was diagnosed with drug-induced parkinsonism and tardive akathisia, found to be coincidentally positive for POLG1 mutation. A literature search on PubMed using the keyword 'POLG1 related parkinsonism' was done. All reported cases were analyzed for this review, and the search revealed 54 cases, including ours, that met our criteria.

Case Report: An 83-year-old male with a past medical history of chronic kidney disease stage III, obstructive sleep apnea, psoriatic arthritis on methotrexate, and depression on mirtazapine; presented with complaints of episodic confusion of 5 years duration and tremors of 2 years duration. He had multiple episodes of confusion associated with clear auditory/visual hallucination and delusions, and a source of infection was always identified. He was taking haloperidol and risperidone during these attacks to control the psychotic symptoms. He developed restlessness (repeated crossing and uncrossing of legs; sitting and standing; moving arms around), three years after starting the antipsychotic medications. The tremors started in his hands bilaterally (right>left), has been stable, present mostly at rest, and doesn't affect his daily activities. On examination, he had symmetric, akinetic, rigid parkinsonism, prominent akathisia, and impaired vibration sense in bilateral lower limbs. We stopped his haloperidol and risperidone and started him on Sinemet. A DaT scan was normal and molecular analysis for POLG1 mutation was positive (E1143G). On follow-up at 85 years of age, he expressed good response to Sinemet, denied any new episodes of delirium, and mentions his akathisia is still present but improving. We diagnosed him with drug-induced parkinsonism and tardive akathisia from antipsychotic use, with a possibly incidental POLG1 mutation.

Conclusion: 1. POLG1 mutation spectrum- Parkinsonism, PEO/ptosis, myopathy, polyneuropathy, ataxia, encephalopathy, epilepsy, cognitive impairment, psychiatric disorders, sensorineural hearing loss, dysarthria/dysphagia, hepatopathy, hypogonadism, cataracts, premature ovarian failure, and so forth. 2. We considered performing a molecular analysis in our patient due to his parkinsonism and recurrent episodes of encephalopathy. A normal DaT scan, however, favored drug-induced parkinsonism. 3. Though the mutation found was possibly incidental, and this particular genotype has not been reported to be pathogenic in literature, it could be a contributing factor to his episodic encephalopathy.

492. A Case of Novel CACNA1A Mutation Causing Type 2 Episodic Ataxia

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Background: The mutation of CACNA1A, a neuronal gene encoding voltage-gated calcium channel has been implicated in episodic ataxia type 2 (EA2), spinocerebellar ataxia type 6, and familial hemiplegic migraine type 1; all autosomal dominant conditions. We present the case of a 55-year-old male, presenting with episodic ataxia who was found to have a novel mutation of CACNA1A and diagnosed with EA type 2.

Case Description: A 55-year-old male presented with complaints of episodic spells of balance difficulties for the last 5 years. Initially, he ambulated normally between spells but gradually developed progressive imbalance. Episodic spells occur at a frequency of 2-3/day, is triggered by the movement of his head or body, or even at rest, and lasts for 15 minutes to 6 hours. It begins with a sudden onset vertigo

and is associated with walking difficulty and slurred speech. He notices some improvement in closing his eyes or lying down. He started using a cane two years ago, as dizziness made ambulating difficult and now relies on a walker mostly, due to progressive baseline walking difficulties. Communication became difficult due to his progressively worsening speech. He was adopted as a child, and his three children are reportedly healthy. On examination, he had a wide-based gait, sways to either side while walking, difficulty with tandem walking, and gaze-evoked nystagmus with a torsional component. Genetic testing revealed a novel, heterozygous, pathogenic variant mutation in the CACNA1A gene (c202 C>T; pR68X). He was diagnosed with EA2 and given acetazolamide. On follow-up, he wasn't sure if it helped with his spells but mentioned a general improvement with his balance. We recommended he keep a log on the frequency, intensity, and duration of episodes for documenting the benefits.

Summary: EA2 is an autosomal dominant disorder that affects all age groups and is characterized by spells of ataxia and gait imbalance lasting hours to days. Patients may experience other symptoms like nausea, vertigo, diplopia, dysarthria, tinnitus, dystonia, and hemiplegia. Migraine and nystagmus can occur, usually in the post-ictal period. To the best of our knowledge, this variant has not been described previously and was not found in the server of the Genome Aggregation Database (http://gnomad.broadinstitute.org/variant/19-13386754-AG-A).

Conclusion: A detailed clinical evaluation can help one come remarkably close to diagnosing the EA type. Our patient encounter pointed to a diagnosis of EA2/3, and genetic testing confirmed EA2.

493. Characterization of the Pattern of Daily Motor Fluctuations in Parkinson's Disease Patients Based on Home Diaries

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Background: Parkinson's disease (PD) patients are often in their best clinical state when attending medical appointments. It is therefore important for clinicians to be familiar with the typical pattern of motor fluctuations that PD patients experience and to obtain a good history regarding potential fluctuations, even when patients are doing well at the time of the evaluation. Using home diary data, this analysis was conducted to characterize PD patients' daily motor status.

Methods: Home diaries from patients from the BIPARK-I trial [Ferreira, *Lancet Neurol*, 2016] with wearing-OFF, despite optimal anti-PD therapy, were used for analyses. Patients' 24-h baseline diary data were evaluated per daily hour. Asleep and ON/OFF fluctuations were characterized and depicted by daily hour. ON/OFF fluctuations were also characterized by daily available hour (i.e., corrected for daily-hour asleep).

Results: A total of 354 patients were included in the analysis. The majority of asleep-time (>50%/h) was within 11pm to 6am. During waking hours (7am-10pm), 4 OFF/ON transition periods were apparent, in line with a higher proportion of patients taking levodopa at 7-8am, 11-12am, ~4pm and 7-8pm . Mean levodopa amount per daily hour intake was ~160mg. When asleep-time was negligible (<5%/h; 9am-9pm): mean OFF-time was ~35% per available daily hour; ON-time ranged from 57-76% per available daily hour; highest ON-time effect was at first ON-period with an apparent lower but stable effect over the remaining hours throughout the day.

Conclusions: For patients enrolled in BIPARK-I, despite optimal anti-PD therapy, at baseline, the prevalence of OFF per daily hour was ~35%. Characterization of patients' daily motor status is desirable for adequate clinical evaluation and for treatment optimization. Understanding the population pattern of daily motor fluctuations may help clinicians identify individual patient fluctuations.

494. Effects of Once-Daily Opicapone on Duration of Overnight OFF and Time to Morning ON in Patients with Parkinson's Disease and Motor Fluctuations

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Background: Two multinational pivotal Phase 3 studies (BIPARK-1 [NCT01568073]; BIPARK-2 [NCT01227655]) were conducted to evaluate opicapone as a once-daily adjunct to levodopa/dopa decarboxylase inhibitor (LD/DDCI) in patients with Parkinson's disease (PD) and motor fluctuations. In both studies, opicapone 50 mg (therapeutic dose) significantly reduced OFF time relative to placebo; it was non-inferior to entacapone, as predefined in BIPARK-1. Since overnight and early morning OFF episodes are significant unmet needs in PD treatment, data from the Phase

3 studies were analyzed post-hoc to evaluate the effects of opicapone 50 mg on duration of overnight OFF and time to morning ON.

Methods: In BIPARK-1 and BIPARK-2, participants received 14-15 weeks of double-blind treatment with placebo, entacapone (BIPARK-1 only), or opicapone in addition to their current levodopa regimen. Based on participants' PD diaries, post-hoc analyses were conducted in those who had overnight (6PM-9AM) or morning (after waking) OFF episodes at baseline. Mean values (±standard error [SE]) at baseline and Week 14/15, along with percent changes from baseline, were analyzed descriptively for opicapone 50 mg and placebo (pooled Phase 3) as well as for opicapone 50 mg and entacapone 200 mg (BIPARK-1).

Results: In the overnight subanalysis for the pooled population (placebo=48, opicapone=67), duration of overnight OFF decreased from baseline (mean±SE [minutes]: placebo=38.1±3.3, opicapone=49.3±4.6) to Week 14/15 (placebo=27.1±6.3, opicapone=23.4±5.1), representing 29% and 52% reductions for placebo and opicapone, respectively. The overnight subanalysis for BIPARK-1 (entacapone=26, opicapone=24) also indicated a decrease (minutes±SE) from baseline (entacapone=43.1±6.0, opicapone=52.1±6.6) to Week 14/15 (entacapone= 23.1±5.6, opicapone=18.8±4.8), representing 46% and 64% reductions in overnight OFF for entacapone and opicapone, respectively. In the morning subanalysis for the pooled population (placebo=210, opicapone= 222), time to morning ON (minutes±SE) decreased from baseline (placebo=89.3±3.7, opicapone= 85.5±3.1) to Week 14/15 (placebo=78.7±4.6, opicapone= 67.0±3.6), representing 12% and 22% reductions for placebo and opicapone, respectively. For BIPARK-1 (entacapone=104, opicapone=101), time to morning ON (minutes±SE) also decreased from baseline (entacapone=90.5±5.9; opicapone= 83.1±4.3) to Week 14/15 (entacapone=79.6±5.6, opicapone= 5.7±5.1), representing 12% and 21% reductions for entacapone and opicapone, respectively. Notably, these positive changes happened in the context of stable or decreased bedtime and nighttime LD/DDCI intake.

Conclusions: Consistent with previously reported effects on daily OFF time, reductions in overnight OFF and time to morning ON from baseline to Week 14/15 were larger with once-daily opicapone 50 mg compared to placebo or entacapone.

495. Incidence and Survival of Psychosis in Patients with Parkinson's Disease (1991-2010)

***Rodolfo Savica, MD PhD**. Mayo Clinic, Rochester, MN, USA.*

Objective: To determine the incidence of psychosis in patients with Parkinson Disease (PD) and to investigate the survival after a psychosis diagnosis among an incident PD cohort from 1991-2010 in Olmsted County, MN.

Background: Psychosis after the onset of PD is a well-known non-motor complication, but few studies have estimated incidence and survival.

Methods: We used the Rochester Epidemiology Project to define an incident cohort study of Parkinsonism from 1991-2010 in Olmsted County, MN. A movement disorder specialist reviewed the electronic medical records (EMR) and applied clinical criterion to diagnose PD. Psychosis was diagnosed using NINDS/NIMH unified criteria. Incidence rates of psychosis were calculated per 100-person years within our cohort of PD patients. The risk of mortality was assessed using a Cox proportional hazards model using the onset of PD as time 0. Onset of psychosis was treated as a time-dependent covariate, and the model was adjusted for sex, age at PD onset, and presence of tremors and bradykinesia. Secondary analysis restricted the cohort to PDP patients only. A cox proportional hazards model was then fit using the onset of psychosis as time 0. Treatment with antipsychotic medication was included as a time-dependent covariate, and the model included the same adjustments as in the primary analysis.

Results: We identified 669 cases of Parkinsonism; among them 297 patients were clinically diagnosed with PD. Of the 297 PD patients, 114 (38.4%) had evidence of psychosis (60% male); the median age of onset of psychosis was 79.4 years. The incidence of Parkinson Disease Psychosis (PDP) was 4.28 cases per 100 person-years. PDP patients had a 71% increased risk of death compared to PD patients (HR=1.71, CI: 1.36-1.80). There was no sex difference in risk of death after psychosis among PDP patients (HR=1.11, CI: 0.71-1.73). Of the 114 patients diagnosed with psychosis, 59 were treated with antipsychotics. There was not any significant difference in survival between treated PDP patients and untreated PDP patients (HR=1.11; CI: 0.72-1.71).

Conclusion: The presence of PDP increased the risk of death compared to PD patients without psychosis. Men with PDP did not have a statistically significant difference in risk of death compared to women with PDP. Lastly, treatment with anti-psychotics did not impact on survival for PDP patients. Further studies in more recent eras are needed to confirm our findings.

496. Risk of Hospital Admission in Patients with Parkinson's Disease Associated Psychosis (1991-2010)

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Objective: To determine indicators for hospital admission in patients with Parkinson's disease (PD) and in patients with Parkinson's disease Psychosis (PDP), and to compare patients treated with anti-psychotics to those untreated in an incident cohort study in Olmsted County, MN.

Background: Few studies have investigated the risk for hospitalizations among PD and PDP patients and the impact of treatment on hospital admissions.

Design/Methods: We used the Rochester Epidemiology Project to define an incident cohort study of parkinsonism from 1991-2010 in Olmsted County, MN. A movement disorder specialist reviewed all the medical records to confirm the diagnoses of PD. We used the NINDS/NIMH unified diagnostic criteria for PDP to differentiate all cases of PDP. A Cox-proportional hazards model was fit using the first record of hospitalization following the onset of PD as the

outcome. A secondary analysis implemented a similar Cox regression, with the first record of hospitalization due to a fall following the onset of PD as the outcome. Psychosis and anti-psychotic treatment were treated as time-dependent covariates in each model. Each model includes adjustments for patient age, sex, and presenting symptoms of PD-tremors and bradykinesia.

Results: Of the 297 incident cases of PD between 1991-2010, 114 (38.4%) met the criteria for PDP at any time-point. The median age of psychosis onset was 79 years (Q1-Q3 73-85; IQR: 12) and the median time between onset of PD and onset of PDP was 8.1 years (Q1= 5.67 Q3= 10.61 and IQR=4.94). Patients with PDP had a 14% (HR = 1.14, p=0.005) increased risk for hospital admission compared to PD patients without psychosis. Among PDP patients, anti-psychotics use (55/110) was not associated with the risk of hospital admissions (HR = 1.10, p = .88). PDP patients had a 41% (HR 1.41, p=0.019) increased risk of hospitalization due to falling compared to PD patients. Among PDP patients, treatment with anti-psychotics was not associated with risk of hospitalization due to falls (HR=1.17, p=0.39).

Conclusions: PDP patients have a 14% greater risk of hospital admission compared to PD patients. Among PDP patients, treatment with anti-psychotic medications was not associated with risk of hospitalization.

497. Association of Co-Morbid Hypertension, Diabetes Mellitus and Body Mass Index in Idiopathic Parkinson's Disease (PD), *LRRK2* Mutation PD and *GBA* Mutation PD

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Objective: To assess medical co-morbidities associated with higher inflammatory states in patients with Parkinson's disease (PD), particularly in those with PD due to *LRRK2* G2019S and glucocerebrosidase1 (*GBA1*) mutations.

Background: Hypertension (HTN), diabetes mellitus (DM) and metabolic syndrome are associated with systemic inflammation and oxidative stress. Animal models of PD, especially in *LRRK2*, support a role for inflammatory factors. Some clinical studies show higher rates of DM and HTN in idiopathic PD (IPD), and non-steroidal anti-inflammatory use in *LRRK2* G2019S carriers has been associated with lower rates of PD.

Methods: To determine possible association between HTN, DM, and a proxy for metabolic syndrome, body mass index (BMI), we evaluated participants with PD in genetic research studies at Mount Sinai Beth Israel. DNA was screened for *LRRK2* G2019S and N370S, L444P, 84GG, IVS2+1G→A, V394L, del55bp, D409H, R496H *GBA*1 mutations. Information regarding BMI, HTN, and DM was obtained using systematic medical history questionnaire, and when available, cross-referenced with clinical record, including medications. Linear and logistic regression analyses adjusting for age and gender were performed to compare BMI and the odds of hypertension and diabetes between groups, respectively. Secondary models were run adjusting for levodopa dose and duration of PD (Stata 16).

Results: *GBA* PD were younger than the others (n, mean age±SD, % women: 90, 66.8±10.5, 41.1%), IPD (285, 71.2±10.5, 34.7%), *LRRK2* PD (91, 72.2±10.7, 46.2%), and *GBA-LRRK2* PD (9, 71.3±9.3 years, 55.6%). Neither the odds of hypertension nor diabetes was different between groups. Hypertension: *GBA-LRRK2* PD (n, % with hypertension: 6/9, 66.7%), *GBA* PD (36/90, 40%), IPD (121/285, 42.5%), and *LRRK2* PD (40/91, 44%); Diabetes: *GBA-LRRK2* PD(1/9, 11.1%), *GBA* PD (8/90, 8.9%), IPD (31/285, 10.9%), and *LRRK2* PD (6/91, 6.6%). In linear regression analysis, BMI was not different between groups: *GBA-LRRK2* PD (mean BMI±SD: 24.4±2.8), *GBA* PD (25.5±4.3), IPD (25.4±4.6), and *LRRK2* PD (25.3±4.2).

Conclusions: The lack of association between HTN, DM, or BMI with any of the genetic cohorts could represent a true lack of association. Alternatively, an effect may be present in the genetic group and non-genetic group that could only be detected by studying controls or by increasing the sample size. Finally, the specific inflammatory pathways may not be as strongly shared between systemic inflammatory disease and brain pathways in PD.

498. Astrocyte-Converted Neurons Rescue Nigro-Striatal Circuit in Parkinson Disease Model

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Parkinson disease is characterized by loss of substantia nigra dopaminergic neurons. Similar to other major neurodegenerative disorders, no disease-modifying treatment exists. While most treatment strategies aim to prevent neuronal loss or protect vulnerable neuronal circuits, a potential alternative is that replacing lost neurons may serve to reconstruct disrupted circuits. Herein we report on an efficient, single-step conversion of isolated mouse and human astrocytes into functional neurons by depleting the RNA binding protein PTB. Applying this approach to the mouse brain, we demonstrated progressive conversion of astrocytes into new neurons whose processes innervated endogenous neural circuits. Astrocytes were converted to neurons in several brain regions; interestingly, the percentage of subtypes differed by region. Using the 6-OHDA model of Parkinson's disease, we demonstrated conversion of midbrain astrocytes into dopaminergic neurons whose axons partially reconstituted the nigro-striatal circuit. Significantly, reinnervation of striatum was accompanied by restoration of dopamine levels and rescue of motor deficits. In preliminary studies, use of antisense oligonucleotides to transiently suppress PTB in midbrain also induced astrocyte conversion to dopaminergic neurons and partially rescued motor phenotypes. These findings identify a potentially powerful and clinically feasible approach to treating neurodegeneration through replacement of lost neurons.

499. Cortical Synaptic and Mitochondrial Dysfunction in Mouse Models of Huntington's Disease

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Huntington's disease (HD) is resulted from the expansion of ployQ tract in the mutant Huntingtin protein (mHTT). Synaptic alteration is one of the earliest manifestations of neuronal dysfunction in HD. However, the mechanism(s) by which mHTT impacts synaptic formation and function remains unclear. Here we used the BACHD and the ΔN17-BACHD models to examine cortical synaptic formation and function in vitro. We established long-term cortical neuronal cultures up till 35 days in vitro (DIV35). we quantitated synaptic formation by immunostaining cultured cortical neurons with specific antibodies against Synapsin I, a pre-synapstic marker and against the 95 kD post synaptic density protein (PSD95), a post-synaptic marker at different stages. Consistent with findings by other investigators, our results have demonstrated that in either WT or HD cortical neurons from both mouse models, synapses began to form at DIV14 and there was no difference between WT and BACHD and between WT and ΔN17-BACHD cortical neurons. However, starting at DIV21 and all the way up to DIV35, BACHD neurons showed a progressive reduction in synapses as compared to WT neurons. Significantly, the synaptic deficits in BACHD neurons were completely mitigated by BDNF treatment; Interestingly, unlike BACHD neurons, the synapses in ΔN17-BACHD cortical neuronal cultures showed a progressive increase as compared to WT neurons. Similar patterns were also observed when we analyzed the mitochondrial membrane potential using JC-9 at DIV8 and DIV13. The mitochondrial membrane potential was lower in BACHD but higher in ΔN17-BACHD cortical neurons than WT neurons. However, cortical neurons from both models showed a significant mitochondrial fragmentation. Taken together, our results have demonstrated that both of BACHD and ΔN17 BACHD cortical neurons showed alteration in synaptic formation, function and mitochondrial activity, albeit the two models displayed opposite effects. Our current study has thus uncovered significant early cellular mechanisms that may contribute to HD pathogenesis.

500. PBT434 Preserves Dopaminergic Neurons, Reduces α-Synuclein Oligomerization, and Improves Motor Function in a Transgenic Murine Multiple System Atrophy Model

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Objective: To characterize PBT434 for disease modification in a mouse model of multiple system atrophy (MSA).

Background: MSA is a fatal neurodegenerative disorder characterized by aggregated α-synuclein in oligodendrocytes and accompanied by neuropathological indicators of oxidative stress and elevated iron in subcortical motor nuclei such as the substantia nigra (SN). Key features of MSA are replicated in the PLP-α-syn transgenic mouse, including progressive striatonigral degeneration and motor deterioration (Refolo et al. Acta Neuropathologica Communications 2018). There are currently no approved treatments for MSA. PBT434 is a novel, orally bioavailable brain penetrant small molecule inhibitor of α-synuclein aggregation with an iron binding affinity competitive for α-synuclein but not for endogenous iron trafficking proteins. In the PLP-α-syn transgenic mouse, PBT434 reduced glial cell inclusions, preserved SN neurons, and improved motor function (Finkelstein American Academy of Neurology [AAN] Annual Meeting, 2019); PBT434 also preserved neurons in multiple Parkinson Disease models (Finkelstein Acta Neuropathologica Communications 2017). In a recently completed Phase 1 study in healthy volunteers, orally administered PBT434 was well-tolerated and displayed dose-dependent pharmacokinetics (Stamler, AAN Annual Meeting, 2020). In the current study, PBT434 was evaluated in the PLP-α-syn transgenic mouse for changes in the number of dopaminergic neurons, in oligomeric α-synuclein, and for altered performance in a motor task for subtantia nigral functioning.

Design/Methods: Six-month old PLP-α-syn transgenic mice received PBT434 in diet or control diet for six months. Motor behavior was evaluated on a modified ("challenging") balance beam test. Brains were evaluated by immunocytochemistry for tyrosine hydroxylase staining of SN neuronal soma and DARRP-32 staining of striatal medium spiny neurons. Midbrain monomeric and oligomeric α-synuclein content was quantified by Western blot.

Results: Consistent with previous findings, PBT434-treated MSA mice demonstrated improved motor performance, with fewer slips per step on the balance beam as compared to control ($p<0.05$). Extending recent findings, PBT434 preserved dopaminergic neurons in the SN pars compacta and DARPP-32-positive neurons in striatum ($p<0.001$). PBT434 reduced the prevalence of oligomeric α-synuclein ($p<0.05$). Preservation of striatal neurons was strongly correlated with attenuation of α-synuclein oligomerization ($p<0.0001$).

Conclusion: Our findings demonstrate the beneficial disease-modifying effect of PBT434 in oligodendroglial α-synucleinopathy on both the motor phenotype and neurodegenerative pathology in the PLP-α-syn transgenic mouse. Paired with the favorable human pharmacokinetic profile, these results support the development of PBT434 for MSA.

501. Genetic Risk Scores and Hallucinations in Parkinson's Disease Patients

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Objective: Non-motor symptoms, such as hallucinations, among Parkinson's disease (PD) patients are common. However, the genetic risk factors for hallucinations in PD remain largely elusive. Here we examine the overlap of genetic architecture for Alzheimer's disease (AD), schizophrenia (SZ), and PD with the genetic architecture for the occurrence of hallucinations in PD.

Methods: We used two population-based studies (ParkWest, Norway, and PEG, USA) providing us with 399 PD patients with European ancestry and with a PD diagnosis after age 55 to assess the associations between four polygenic risk scores (PRS) and hallucinations after five years of mean disease duration. Based on existing GWAS of other cohorts, four PRS were created: one each using AD, SZ, and PD cohorts and another PRS for height, which served as a negative control.

Results: A higher prevalence of hallucinations was observed with each standard deviation increase of the AD-PRS (OR: 1.37, 95%CI: 1.03-1.83; P-value 0.03). This effect was mainly driven by *APOE* (OR: 1.92, 95%CI: 1.14-3.22; P-value 0.01). In addition, a suggestive decrease and increase, respectively, in hallucinations prevalence was observed with the SZ-PRS and the PD-PRS (OR: 0.77, 95%CI: 0.59-1.01; P-value 0.06; and OR: 1.29, 95%CI: 0.95-1.76; P-value 0.11, respectively). No association was observed with the height PRS (OR: 1.00, 95%CI: 0.74-1.35; P-value 0.98).

Conclusions: These results suggest that mechanisms for hallucinations in PD may be driven by the some of the same genetic architecture that leads to cognitive decline in AD, especially by *APOE*.

502. Mortality in Patients with Parkinson Disease Psychosis Receiving Pimavanserin and Quetiapine: A Retrospective Review

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Background: Parkinson's disease (PD) psychosis (PDP) is a disabling non-motor feature associated with higher healthcare utilization, institutionalization, and mortality (Wetmore, *Parkinsonism & Related Disorders*, 2019). PDP treatment is limited to the few antipsychotic medications that do not worsen parkinsonian symptoms; these include quetiapine, clozapine, and pimavanserin (Seppi, *Movement Disorders*, 2019). However, the Food and Drug Administration issued a black box warning for all of these medications, suggesting that elderly patients treated for psychosis have elevated morbidity and mortality. We previously demonstrated that among 676 PD patients, those treated with pimavanserin had lower mortality than those treated with quetiapine or pimavanserin and quetiapine combination therapy (Moreno, *Neurology*, 2018). However, given methodologic limitations, the factors contributing to these mortality differences were unknown.

Objective: To conduct an in-depth retrospective review of the various clinical, iatrogenic, and demographic factors associated with increased mortality in patients treated for PDP.

Method: After obtaining IRB approval, we extracted identified data from the electronic medical record. Patients included were: 1) clinically diagnosed with PD (using ICD-10 code), and 2) seen in the UC San Diego Health System between April 29, 2016 and April 29, 2019. We excluded patients with psychiatric diagnoses (e.g., bipolar disorder, schizophrenia) or atypical parkinsonism (e.g., multiple system atrophy, drug-induced parkinsonism). We categorized patients according to PDP treatment: none (controls), pimavanserin, quetiapine, or both pimavanserin and quetiapine (combination). Applying chi-square statistical analysis with post hoc Tukey Honest Significant Differences, we compared mortality between groups.

Results: Using more stringent eligibility criteria, our sample size included 2,993 PD patients: 2,680 controls, 41 receiving pimavanserin, 191 receiving quetiapine, and 70 receiving the combination. We excluded patients treated with clozapine monotherapy or other antipsychotic combinations from analyses due to low sample size (n=11). Group mortality rates were: controls=7.5%; pimavanserin=13.6%; quetiapine=17.8%; and combination therapy=17.1%. Compared to controls, the quetiapine group and combination group had higher mortality ($p<0.001$ and $p=0.006$, respectively). The mortality rate of pimavanserin was similar to controls ($p=0.212$).

Conclusion: We replicated our earlier work showing that PDP patients treated with pimavanserin had similar mortality compared to untreated controls, while those treated with quetiapine and both agents had higher mortality rates. Further work is being done to analyze detailed risk factors in these populations to identify potential clinical characteristics, medications, medical comorbidities, laboratory abnormalities, and demographic features that are associated with mortality.

503. Early-Onset Parkinson Disease Screening in Patients from Nigeria

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Nigeria is one of the most populated countries in the world and is approximated to have about 7 million Nigerians that are 65 years of age or older. The steady increase in the elderly population has resulted in the increase in interest to perform studies to identify the prevalence and causes of PD within the population. The estimated prevalence of PD in Nigeria is estimated at 10-235 per 100000 persons. Previous reports of

this PD cohort concentrated primarily on prevalence, clinical symptoms, environmental risks factors, other diseases mimicking the clinical features of PD and biochemical or pathological findings with a very limited number of studies investigating the genetic etiology of PD. The aim of this study was to screen early onset PD patients from Nigeria for the established pathogenic early onset PD genes: *PRKN*, *PINK1* and *DJ1* to identify any known pathogenic mutations or novel mutations that could be specific to the Nigerian population. All EOPD patients (n=15) were bi-directionally Sanger sequenced for all coding regions of *PRKN*, *PINK1* and *DJ1*. Exon dosage analysis was performed with multiplex ligation-dependent probe amplification. The Sanger sequencing in 15 EOPD patients identified 22 variants across the 3 genes: *PINK1* n=10, *DJ1* n=3, and *PRKN* n=9 of which none were pathogenic. Neither exonic duplications nor deletions were identified within the cohort. Our preliminary screening did not identify any known pathogenic mutations nor identify any novel mutations suggestive as being pathogenic or a risk factor. The lack of genetic findings within these genes does not suggest their lack of importance within the Nigerian population but instead the need to increase sample size and continue further genetic screening in Nigerian populations. Perhaps whole genome sequencing for samples that are negative for pathogenic mutations can identify further regions of interest within the genome specific to the population.

504. The Association between *SNCA* Gene Top Parkinson's Disease Variants and Basal Ganglia Imaging Traits

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Objective: To investigate the neuroimaging correlates of the top three independent alpha-synuclein (*SNCA)* common genetic variants associated with Parkinson's disease (PD): rs356182 (the top PD risk variant at the 3' region), rs763443 (a secondary independent risk PD variant at the 5' region), and rs2870004 (a novel and independent risk variant at the 3' region).

Methods: We evaluated de novo PD patients from the Parkinson's Progressive Markers Initiative (PPMI) with available *SNCA* genotype, basal ganglia dopamine transporter (DAT) availability [as measured by ^{123}I-FP-CIT SPECT (n = 381 PD patients)], and T1-weighted 3T brain MRIs (n = 143 PD patients). Using a region-of-interest approach, we analyzed the mean and asymmetry index [AI= | left - right |/(left + right) * 100] of the basal ganglia regional DAT availability and volume measures as well as regional alterations in structural morphology. We applied linear regression models to compare risk allele carriers of each of the top three PD-associated *SNCA* common variants to non-carriers. In each model, the following covariates were included: age, gender, ethnicity, imaging sites, intracranial volume, and disease-related factors.

Results: A significant increase in the putaminal asymmetry index of ^{123}I-FP-CIT availability was identified in PD patients homozygous for the rs356182 (p = 0.009) or a proxy for the rs763443 (p = 0.006) risk alleles relative to non-carriers. Further, a significantly reduced putamen volume was identified in carriers (homozygous and heterozygous combined) of the rs356182 risk allele compared to non-carriers. In contrast, carriers of a proxy for rs763443 risk allele exhibited a significant reduction in globus pallidus volume compared to non-carriers (p =0.001). This was reflected by the structural morphology findings, which revealed regional atrophy within the posterio-medial and inferior regions of putamen and globus pallidus in carriers of rs356182 and a proxy for rs763443 risk alleles. No significant differences were evident in basal ganglia DAT availability or structural measures in carriers of a proxy for rs2870004 risk allele relative to non-carriers.

Conclusion: The two top PD *SNCA* common variants, rs356182 and rs763443, are associated with asymmetric putaminal dopamine availability and distinct basal ganglia atrophy in early PD. These relationships to disease-specific intermediate (subclinical) phenotypes highlight the relevance of such *SNCA* common variants to PD's underlying mechanisms.

505. Understanding the Interaction between Gut Microbiome and the Brain through Machine Learning Based Modeling

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This work demonstrated the use of machine learning techniques and massive graph databases to support meta-analysis and meta-study of research papers and other publications discussing the interaction between gut microbiome and the brain. The neurological effects of gut microbiome have been a topic of research for more than a decade with numerous publications and research works. Recent research in movement disorders such as Parkinson's disease indicates that gut microbiome plays an important role in early stages of the disease. Some researchers even suggest that Parkinson's disease starts in the gut. Other published research works indicate a relationship between gut microbiome and neurological diseases such as Alzheimer's as well as psychiatric disorders related to depression and anxiety. Our presentation describes the use of machine learning techniques, graph databases and graph visualization methods to build a multisystem model of the interaction between the brain and the gut microbiome. Our work identifies the most promising gut microbes and related signaling molecules for medical use in neurology. We accomplished that by deploying natural language processing (NLP) techniques in searching public databases, such as PubMed and Google Scholar. Our data science tools automatically search for published work and research papers related to specific gut microbiome relevant to neurology in animal, human and in-vitro models, extracting data and

creating the multisystem model. Our work is expected to help guide research in manipulation of gut microbiome to support therapies in neurology.

506. COPD/Asthma and Active Smoking History Associates Independently with Parkinson's Disease Outcome in an Essential Tremor Population

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Cigarette smoking has consistently been shown to be negatively associated with the later development of Parkinson's disease (PD)[1]. The relationship between COPD and PD is less clearly understood. Emerging evidence suggests that the β_2-adrenoreceptor may modulate the α-synuclein gene[2] suggesting one possible independent pathway that COPD/Asthma may relate to PD via its treatment. We wished to evaluate the relationship between COPD/Asthma and PD further while controlling for any confounding effect of active smoking history, specifically in Essential Tremor (ET) patients who are at increased risk for the development of PD than the general population[3]. We performed a retrospective cohort study from Geisinger Health System, which serves a stable rural population from central Pennsylvania. Exclusion criteria included those with secondary, vascular, or atypical PD. We excluded any PD diagnosis made on or before the diagnosis of ET. The index date, that is, the date at which follow-up time started was determined based on when ET began. Comparison across groups was computed using Cox proportional hazard model treating time until PD development as the outcome and censoring follow up time at the date of the last encounter. The proportional hazards assumption was tested and confirmed. We identified a total of 3226 patients with ET, of which 331 later developed PD. A neurologist made both diagnoses. The Hazard Ratio (HR) for COPD/Asthma was 0.63 (95% CI 0.49 to 0.81) and 0.45 (95% CI 0.27 - 0.75) for active smoking status. The model was adjusted for age, gender, history of appendectomy, hyperlipidemia, Diabetes Mellitus type 2, hypertension, stroke, family history of tremors and/or parkinsonism, constipation, depression, and anxiety. From this preliminary data, active smoking status and COPD/Asthma history were independently and negatively associated with PD in our patients with ET, with a 55% and 37% lower hazard, respectively. This suggests that some aspect(s) of the pathology, treatment, or other attributes of COPD/Asthma may provide an alternative protective pathway from smoking. However, our analysis did not distinguish which event (exposure or outcome) came first. This relationship will need further investigation to elucidate the exact mechanism of possible protection in ET patients and whether this negative relationship exists in the general population. 1. Xiao Li. *Archives of Gerontology and Geriatrics*. 2015 2. Shuchi Mittal. *Science*. 2017 3. Mary Ann Thenganatt. *Parkinsonism and Related Disorders*. 2016

507. Impact of Race and Socioeconomic Status on the Utilization of Advanced Therapies in Parkinson's Disease

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Objective: Using a multi-site registry of Parkinson's Disease (PD) patients, we assess the impact of race, ethnicity, and socioeconomic status (SES) on the utilization of deep brain stimulation (DBS) and carbidopa-levodopa enteral suspension (Duopa), in the treatment of PD.

Background: DBS and Duopa are used as options when levodopa therapy is limited by side effects. Past studies have shown that Black and Asian patients as well as Medicaid users are less likely to receive DBS. There is a lack of research into the demographics of patients using Duopa.

Design/Methods: Using the Parkinson Foundation Quality Improvement Initiative (PF-QII) registry, we used chi-squared analysis to assess for differences in advanced therapy utilization by race and ethnicity, then used the Cox regression model to control for multiple covariates. We also assessed average household income by zip code which was used as a surrogate for SES.

Results: A total of 11,588 patients were analyzed. At any given time post-PD diagnosis, Black and Hispanic patients were 70% and 25% less likely, respectively, to receive DBS compared to White patients ($p<0.0001$, $p=0.05$). Although the sample size was too small to assess for statistical significance, of the 104 Duopa recipients in the database, none were Black and two were Hispanic/Latino. Income was not statistically significant after controlling for covariates ($p = 0.51$).

Conclusion: Black and Hispanic/Latino PD patients are significantly less likely to receive DBS compared to White patients. While limited by sample size, none of the Black patients in the registry received Duopa therapy. Average household income was not a significant factor, although a multifactorial surrogate for SES may be necessary for future analysis. It will be important to develop strategies to increase education and outreach to the PD minority community to address the inequities in the use of advanced PD therapeutics.

508. Amantadine Therapy for Ataxia Management in Patients with Spinocerebellar Ataxia Type 7

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Background: Spinocerebellar ataxia type 7 is a rare autosomal dominant disorder characterized by progressive cerebellar ataxia and retinal degeneration resulting in blindness, a unique feature amongst the dominantly inherited SCAs. The disease is caused by expansion of a polyglutamate (CAG) repeat within the SCA7 gene in the chromosome 3p, which encodes a protein named ataxin-7. The phenotypic expressions may vary widely based on the CAG repeat count and age of onset, an expansion of > 37 CAG repeats is pathogenic. SCA7 displays variable penetration and marked anticipation of both onset age and rate of progression. To date, there are no approved medications for the treatment of this condition; however there are a variety of possible targets for ataxia treatment.

Case: We report a 16-year-old male with progressive visual loss since age 12 followed by dysarthria, limb and gait ataxia,

shuffling gait to the point of requiring a walker. He was evaluated by an ophthalmologist who diagnosed him with rod-cone dystrophy. MRI brain at age 13 showed mild diffuse cerebellar atrophy. Genetic SCA panel detected 64 CAG repeats in the SCA7 gene, confirming the diagnosis of SCA7. He had no known family history of vision loss or ataxia. The patient presented to our institution at age 16. Exam revealed decreased visual acuity, slow saccades, limited vertical gaze, severe dysarthria, appendicular ataxia, dysmetria and adiadochokinesia. He was wheelchair-bound and was not able to stand without assistance. The Scale for the Assessment and Rating for Ataxia (SARA) score was 37. Amantadine 100mg daily was initiated and after 4 weeks of treatment patient and family members reported significant improvement, especially in truncal ataxia. SARA score at that time was 31, indicating an improvement of 16%. Subsequently, amantadine was increased to 100mg twice daily. A follow up visit is pending.

Discussion: Amantadine, an antiglutaminergic medication, has been reported to have mild-to-moderate improvement in symptoms of ataxia and parkinsonism in patients with ataxia telangiectasia. This is the first case reporting improvement of ataxia in a patient with SCA7. This report suggests that amantadine may be useful in the treatment for ataxia in patients with SCA7. Further large-scale studies are needed to confirm these results.

509. Sleep and Depression in Parkinson's Disease: Investigating the Relationship between Sleep and Depression Using a Combination of Subjective and Objective Sleep Assessment Methods

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Introduction: Sleep disturbances are among the most common of the non-motor symptoms of Parkinson's Disease (PD) and are strongly associated with depressive symptoms. Sleep quality can be assessed using both subjective and objective measures. Studies have shown that subjective sleep quality often differs from objective parameters. Few studies have used a combination of subjective and objective methods to explore the relationship between sleep quality and depressive symptoms.

Aims & Objectives: The aim of this study was to compare subjective and objective sleep measures and explore how these relate to depressive symptoms in a PD population. Methods Thirty-seven community-dwelling PD patients were included in this study. The Pittsburgh Sleep Quality Index (PSQI) and wrist-actigraphy were used to assess subjective and objective sleep quality, respectively. Participants wore the wrist-actigraph for seven consecutive days. The Beck Depression Inventory (BDI) was used to measure depressive symptoms.

Results: Weak to non-significant correlations were found between PSQI scores and actigraphy-determined sleep parameters. BDI score was significantly related to PSQI subjective sleep quality ($r=0.62$, $p<.0001$), sleep latency ($r=0.53$, $p<.001$), sleep disturbances ($r=0.61$, $p<.0001$), daytime dysfunction ($r=0.51$, $p<.002$), and global score ($r=0.73$, $p<.0001$). BDI score did not correlate with any of the actigraphy-determined sleep parameters.

Conclusions: These results suggest that a patient's perception of sleep quality is inconsistent with objective parameters. Interestingly, subjective measures were associated with depressive symptoms while objective parameters were not. This study further highlights the complexity of sleep dysfunction in Parkinson's Disease.

510. Altered Capicua Expression Drives Regional Purkinje Neuron Vulnerability Through Ion Channel Gene Dysregulation in Spinocerebellar Ataxia Type 1

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Selective neuronal vulnerability is a ubiquitous feature of neurodegenerative disease, yet it remains poorly understood. Efforts to understand the mechanisms that differentiate affected and unaffected neurons can be frustrated by the numerous differences between cell types, presenting challenges to unbiased pathway discovery. Using the ATXN1 [82Q] model of spinocerebellar ataxia type 1 (SCA1), we took advantage of the well-defined lobular architecture of the cerebellar cortex to test the hypothesis that regional differences in Purkinje neuron degeneration can provide novel insights into selective vulnerability. Comparison of Purkinje neuron degeneration between the anterior cerebellum (lobules II-V) and the nodular zone (lobules IX-X) revealed that anterior Purkinje neurons degenerate earlier than those from the nodular zone in ATXN1[82Q] mice. Given the established role for electrophysiologic dysfunction in the pathogenesis of SCA1 and other ataxias, whole transcriptome datasets were mined for shared ion channel genes, revealing a group of channel genes already linked to ataxia. Dysregulation of these channel genes (*Cacna1g*, *Trpc3*, and *Kcnma1*) was found to be unique to the anterior cerebellum, while other disease-associated transcripts showed no regional effects. Purkinje neuron hyperexcitability was also found to be unique to the anterior cerebellum, demonstrating that channel gene dysregulation and electrophysiologic dysfunction were well-correlated with regional Purkinje neuron degeneration. Efforts to understand the basis for selective dysregulation of channel transcripts in the anterior cerebellum revealed modestly increased expression of the ATXN1 corepressor Capicua (Cic) in anterior cerebellar Purkinje neurons. Importantly, lentiviral overexpression of Cic in the nodular zone accelerated both aberrant Purkinje neuron spiking and neurodegeneration. These findings reinforce the central role for Cic in SCA1 cerebellar pathophysiology and suggest that only modest reductions in Cic are needed to have profound therapeutic impact in SCA1. Furthermore, they validate the use of cell subtype-level analysis for pathway discovery in

neurodegenerative disease, which is likely to have broad implications beyond SCA1 and other ataxias.

511. Investigating a Novel Combination of Sensory Markers in Cervical Dystonia

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Background: Cervical Dystonia (CD) is a neurological condition causing involuntary contractions in the neck musculature, experienced as pulling or spasmodic sensations. 'Sensory tricks', such as touching the face or neck, that seem to ameliorate the involuntary movement, hint at a non-motor component to CD (Stacy, *Neurologic Clinics*, 2008). Impairments in four sensory markers are common in patients with CD: spatial discrimination threshold (SDT), temporal discrimination threshold (TDT), vibration induced illusion of movement (VIIM), and kinesthesia (Molloy, *Brain,* 2003; Bradley, *Journal of Neurology,* 2012; Frima, *Movement Disorders,* 2008; Putzki, *Movement Disorders,* 2006). No reports exist of all four markers being evaluated in the same CD cohort. This study's objective was to determine whether combinations of these four markers are more prevalent in patients with CD than in healthy controls.

Methods: This study enrolled 15 patients with CD and 15 healthy controls. Participants underwent a brief neurological exam conducted by a movement disorders specialist before being evaluated through a series of noninvasive tests. SDT, VIIM, and kinesthesia tests were performed bilaterally and scored by dominant hand. Any incorrect kinesthesia response was considered abnormal. All SDT, TDT, and VIIM measures were converted to standardized Z scores with scores > 2.0 considered abnormal. Fisher's exact test compared proportions of abnormal scores per test between patients with CD and controls.

Results: Eighty percent (12/15) of the CD patient cohort reported using sensory tricks. The average age of patients with CD was 62.7 ± 8.7 years, with disease duration of 15.0 ± 7.2 years. The average age of the control group was 44.8 ± 13.1 years. More patients with CD had abnormal scores for SDT ($p = 0.04$), TDT ($p = 0.05$), and kinesthesia ($p = 0.06$) compared to controls, but no significant difference was found for VIIM ($p = 0.48$). Eighty percent of patients with CD (12/15) had abnormal scores, with 7 demonstrating impairment in one sensory domain, 3 demonstrating impairment in two domains, and 2 demonstrating impairment in three domains. In the control group, only 20% (3/15) had an abnormal score, and none had more than one.

Conclusions: This study is the first to evaluate four sensory markers in a single cohort of patients with cervical dystonia. Future studies with greater sample sizes are needed to determine whether screening for combinations of non-motor symptoms could facilitate earlier and more accurate diagnoses of focal dystonias.

K-579. *APOE* Genotype Regulates Pathology and Disease Progression in Synucleinopathy

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APOE e4 genotype increases risk of dementia in Parkinson disease (PDD) and dementia with Lewy bodies (DLB) but the mechanism of this association is not clear, as patients with PDD and DLB often have a mixture of alpha-synuclein (aSyn), amyloid-beta (Abeta), and tau pathologies. *APOE* e4 exacerbates brain Ab pathology, as well as tau pathology, but it was not previously clear whether *APOE* genotype independently regulates aSyn pathology. In this study we generated A53T aSyn transgenic mice (A53T) on *Apoe* knockout (A53T/EKO), or human *APOE* knock-in backgrounds (A53T/E2, E3, E4). At twelve months of age, A53T/E4 mice accumulated higher levels of detergent-insoluble phosphorylated aSyn in the brainstem compared to A53T/EKO and A53T/E3; levels in A53T/E2 mice were undetectable. By immunohistochemistry, A53T/E4 mice displayed a higher burden of phosphorylated aSyn inclusions and reactive gliosis compared to A53T/E2 mice. Gene expression analysis indicated that glial-mediated inflammation correlated strongly with the presence of aSyn pathology, but did not directly correlate with *APOE* genotype. Expression of genes associated with myelination was negative correlated with aSyn pathology but positively correlated with *APOE2* genotype. Behavioral analysis showed delayed onset of motor deficits in A53T/E2 mice, and A53T/E2 mice survived longer compared to other *APOE* genotypes. In a complementary model of aSyn spreading, striatal injection of aSyn pre-formed fibrils resulted in increased accumulation of aSyn pathology in the substantia nigra of A53T/E4 mice compared to A53T/E2 and A53T/EKO mice. Among human patients with PD, *APOE* e4/e4 individuals showed the fasted rate of cognitive decline, while *APOE* e2/e2 individuals remained stable over time. Our results demonstrate that *APOE* genotype directly regulates aSyn pathology independent of its established effects on Abeta and tau and suggest that *APOE* e2 may confer protection against aSyn aggregation and neurodegeneration in synucleinopathies.

K-580. Glucocerebrosidase Deficiency Mediates Propagation Of Protein Aggregation In A*Drosophila*Model Of Neurodegeneration Via Modification Of Extracellular Vesicles

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Parkinson's disease (PD) progression correlates with temporo-spatial distribution of protein aggregates in the brain, suggesting that a mechanism underlying propagation of protein aggregates can be perturbed to affect the rate of progression of neurodegeneration. Mutations in the gene *glucosidase, beta acid 1* (*GBA*) are not only the most penetrant genetic risk factor for PD and dementia with Lewy bodies, but also accelerate the progression of symptoms in PD[6-9]. Our work and others recently revealed that mutations in *GBA* lead to dysregulation of EVs, leading us to hypothesize that *GBA* mutations may accelerate disease progression by promoting the spread of protein aggregation from cell to cell via dysregulated EVs.Using a previously developed *Drosophila* model of *GBA* deficiency (GBA^{del}) manifesting multiple phenotypes, including neurodegeneration and accelerated protein aggregation, we used standard *Drosophila*reagents, immunohistochemistry and Western blotting to evaluate protein aggregation. We isolated EVs <220 nm in diameter from *Drosophila* hemolymph per published protocol.We examined whether tissue specific expression of wildtype *GBA* could rescue the accelerated protein aggregation present in homozygous GBA^{del} flies. Expressing wildtype *GBA1b* in muscle rescued insoluble ubiquitinated protein and Ref(2)p accumulation in brain as well as muscle. Neuronal expression of wildtype *dGBA1b* also rescued ubiquitinated protein and Ref(2)p aggregation in both brain and muscle. Non-cell autonomous rescue of protein aggregates in brain was also observed with expression of human wildtype *GBA*in muscle.EVs isolated from GBA^{del} flies have increased levels of Ref(2)p and ubiquitinated proteins compared to control flies. Expression of wildtype d*GBA1b* or human *GBA* in muscle suppressed increased levels of Ref(2)p and ubiquitinated proteins in GBA^{del} flies, and human glucocerebrosidase was found in EVs of flies expressing human *GBA*. Our results suggest that GBA deficiency mediates PD pathogenesis by accelerating propagation of protein aggregates through dysregulation of EV protein cargo. Elucidating this novel mechanism for GBA will have important implications for disease-modifying treatment of GBA-associated diseases and other aggregate-prone neurodegenerative diseases.

Multiple Sclerosis

168. The Power of Single Cell Technologies; from T Cell Receptor to Antigen(s) in Multiple Sclerosis

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The role of T cells in Multiple sclerosis (MS) is well established. Long-standing quest in MS is to determine key T cell antigen(s), which drive the initial response. Objective here is to comprehensively understand of the T cell receptor (TCR) repertoire in MS with a focus on identifying dominant T cell clones. Major bottleneck in understanding T cell responses in health and disease is the diversity of TCRs and the vast variety of antigens that they can encounter. We have taken a sequence-based approach to T cell responses and developed a robust single T cell paired TCR sequencing and phenotyping method and a bioinformatic analysis pipeline, which can group TCR sequences into clusters sharing specificity. Further, we have developed unbiased highthrouhput technology (yeast peptide-HLA library) to determine antigen specificity of TCRs. By using single cell paired TCR sequencing and mass spectrometry-based cytometry (CyToF), we have analyzed both MS patients and healthy controls (HC) with respect to their overall immune system and the specific T cell types. At a single cell level, we have analyzed TCR repertoire and phenotype (using 10X genomics) of brain homing, activated CD4, CD8, and gd T cells from the blood and CSF of 28 recent onset untreated MS patients and found significant T cell clonal expansion which is not seen in HCs. We find shared TCRs between blood and the CSF in MS patients and in CSF, CD8 TCRs are highly clonal. Moreover, we find convergence of TCRs between MS patients suggesting of TCRs with shared specificity. Using yeast displayed peptide-HLA library which contains a billion peptide antigens, we have screened expanded CD4 TCRs from HLA-DR*1501 homozygous MS patients and found ligands. Some of the peptides identified resemble viral peptides and these can activate primary CD4 T cell clones from MS patients and cross-react with myelin basic protein. Our study highlights the value of studying T cell specificity and activity from 'the bottom up'; that is, identifying the T cells that are most active in MS or any disease by TCR sequencing, using activation markers and clonal expansion as key indicators, and ligand identification either with a yeast library or candidate antigens and reporter cell lines transfected with the relevant TCR pairs. This is very much in contrast to traditional methods that typically involve knowing what the relevant antigens are.

169. Evaluating the Relative Contributions of Various Domains on Fall Rates Cross-Sectionally and Longitudinally in Persons with Multiple Sclerosis

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Background: Falls are a common and impactful health concern in persons with multiple sclerosis (MS). As such, it is crucial to understand the processes that contribute to falls in this population. Reactive postural control—how one responds to a sudden perturbation in balance—is likely an important factor for fall risk; however, the specific relationship between reactive posture and fall risk is poorly understood in persons with MS.

Specific Aim: The aim of this study is to determine whether delays in lower-extremity muscle activity after balance perturbations predict fall rates among those affected by MS, while accounting for clinical, functional, sensory, psychological, and cognitive factors.

Method: At baseline of the 18-month-long study, 122 participants with MS were included. Assessments were conducted every 6 months (t = 4). Demographic, clinical, balance, mobility, cognitive, and psychological constructs were measured to evaluate their relationships with fall rates. Cross-sectional analysis at baseline was performed using negative binomial regression. Random effects negative binomial regression was performed to evaluate longitudinal relationships.

Results: Cross-sectionally, Timed Up-and-Go times, scores on the Falls Efficacy Scale - International (FES-I), and muscle onset latency after perturbations were significant predictors of retrospective falls rates. Longitudinally, trait-level FES-I, and muscle onset latency were significant predictors for falls rates, as was the trait measure for Stroop Color-Word performance.

Conclusion: Delays in automatic postural responses seem to account uniquely for fall rates in this population—beyond clinical, balance, or mobility measures. As such, these delays may contribute to the increased fall rate in people with MS compared to neurotypical adults. In addition to brief self-report instruments (FES-I) and cognitive assessments, muscle onset after balance perturbations may be a valuable tool for predicting falls in those with MS.

170. Vestibular Function and Fatigue in People with Multiple Sclerosis

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Introduction: People with multiple sclerosis (PwMS) commonly report fatigue and balance impairments as two of their most severe symptoms with the greatest impact on their quality of life. Studies of vestibular rehabilitation in PwMS suggest that vestibular rehabilitation improves not only balance function but also fatigue, hypothesizing that these symptoms share common central sensory pathways. However, balance requires the integration of several sensory systems, not only vestibular. The purpose of this study is to complete a robust examination of clinical measures of vestibular function in PwMS and investigate whether those functions relate to self-reported fatigue, walking ability, and balance performance.

Methods: 40 PwMS and 20 people without MS, ages 21-55, will be recruited for 3 hours of vestibular, balance, and walking testing (two 1.5 hour sessions). PwMS with a diagnosis of relapsing-remitting MS and EDSS score of <=6.5 will be eligible. EDSS scores will be determined by the Neurostatus-C certified PI. The testing battery consists of fatigue surveys, rotary-chair eye-tracking measures, computerized dynamic visual acuity (DVA), video head-impulse testing (vHIT), cervical and ocular vestibular-evoked myogenic potentials (cVEMP and oVEMP), Sensory Organization Test (SOT), Functional Gait Assessment (FGA), and 6-Minute-Walk (6MW). Performance on these measures will be compared across EDSS severity and between PwMS and people without.

Results: 26 PwMS have completed testing with an average age of 42 and average EDSS score of 3.0. Dividing the sample into EDSS groups of <3 or >=3 creates groups of n=14 and n=12. The >=3 EDSS group had significantly worse performance on functional measures of vestibular function such as DVA, SOT, and subjective visual vertical (SVV), but there were no differences in reflexive vestibular function such as the vestibular ocular reflex nor VEMPs. The higher EDSS group exhibited lower 6MW distances and FGA scores. Combining data from all 26 PwMS, there were significant Spearman correlations between 6MW distance, DVA, SOT, FGA and SVV. Self-reported fatigue was significantly correlated with 6MW distance, FGA, and SOT, but no other measures.

Discussion: While collection is ongoing, current data suggests that central, but not reflexive, vestibular function, worsens over disease severity in PwMS. Self-reported fatigue appears related to physical function through the 6MW, FGA, and SOT tasks but not related to other vestibular measures. However, 6MW, which may be seen as a measure of objective physical fatigue is correlated with these less physically demanding vestibular tasks.

171. Continued Increase of Multiple Sclerosis and Neuromyelitis Optica in Japan: Updates from the 5th Nationwide Survey

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Backgrounds: In Japan, nationwide survey for multiple sclerosis (MS) has regularly been conducted since 1972, and the past 4 surveys conducted before the discovery of anti-aquaporin 4 antibodies demonstrated the rapid increase of MS.

Objective: To investigate the epidemiological characteristics of MS and neuromyelitis optica spectrum disorders (NMOSD) in Japan through the 5th nationwide survey.

Methods: Preliminary survey was conducted to ascertain the approximate number of patients with either MS or NMOSD who had seen at the selected facilities during 2017. Preliminary survey packages were sent to departments of neurology, internal medicine, ophthalmology, and pediatrics, at the facilities randomly selected using pre-determined sampling rates according to the stratification based on the number of hospital beds, as well as those specifically focused on these diseases. Secondary questionnaire was sent to the facilities which replied that they saw those patients in 2017 to collect the detailed clinical information of each patient.

Results: Out of 3,799 departments where we sent preliminary survey, 2,284 (60.1%) replied and 645 departments reported the presence of the patients with the diseases. Second questionnaire form was sent to the 645 departments for 13,067 cases, and 6,990 (53.5%) forms were returned for further analysis. Estimated number of MS and NMOSD patients were 24,118, which is more than 10-fold higher than that (2,280) of the 1st survey in 1972. The crude prevalence for MS and NMOSD was 19.6/100,000 (14.3 for MS and 5.3 for NMOSD). Male:female ratio was 1:2.2 in MS and 1:4.4 in NMOSD. The onset age (mean±standard deviation, year) was 32.3±11.6 in MS and 44.2±16.1 in NMOSD, and the disease duration (year) was 12.9±9.0 in MS and 10.9±9.5 in NMOSD. The Expanded Disability Status Scale scores were 2.7±2.4 in MS and 3.7±2.4 in NMOSD. Disease-modifying therapy had been used for 77.2% in MS (37.2% in the 4th survey in 2003).

Conclusions: As the combined prevalence of MS and NMOSD was 7.7/100,000 in the 4th survey (4.4 for conventional MS and 3.3 for others including opticospinal form), the prevalence of both MS and NMOSD appears to be still increasing. The prevalence of NMOSD is the second highest following Martinique. Disease severity may have become milder in MS and NMOSD compared with the 4th survey (3.5±2.9 in conventional MS and 4.3±2.7 in opticospinal form), though the disease durations in the two studies were comparable.

172. Vascular Comorbidity is Associated with Lower Brain Volumes in a Large Multiple Sclerosis Cohort

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Background: Vascular comorbidities like diabetes, hypertension and dyslipidemia are overrepresented in people with multiple sclerosis (MS) and may contribute to adverse MS outcomes. Existing studies evaluating vascular comorbidity and MS course were often limited by relatively small sample sizes or lack of large-scale corresponding quantitative neuroimaging studies.

Objective: To assess the association between vascular comorbidity burden with clinical and imaging features of disease severity in a large population of people with multiple sclerosis (MS).

Methods: We included participants from the Multiple Sclerosis Partners Advancing Technology Health Solutions (MS PATHS) cohort. We evaluated if metabolic and vascular comorbidities (diabetes, hypertension and dyslipidemia) or a composite sum of vascular comorbidities was associated with MS characteristics, including objective neurologic function assessments and quantitative brain MRI measurements, after adjusting for covariates using propensity score weighted models.

Results: 11,506 participants (6409 [55%] with brain MRI) were included in the analysis. Individuals with 2+ vascular comorbidities had slower walking speed (-0.49 SD times slower; 95% CI: -0.78 to -0.19; p=0.001), slower manual dexterity (-0.41 times slower; 95% CI: -0.57 to -0.26; p<0.0001), and fewer correct scores on cognitive processing speed (-0.11 SD; -0.20 to -0.02; p=0.03) relative to those with none of these comorbidities. Those with 2+ had lower brain parenchymal (-0.41%, 95% CI -0.64%, -0.17%) and gray matter fractions (-0.30%, 95% CI -0.49, -0.10), including reduced cortical (-10.10 mL, 95% CI -15.42, -4.78) and deep (-0.44 mL, 95% CI -0.84, -0.04) gray matter volumes, when compared to those with no comorbidity. Comorbidity burden was not associated with T2 lesion volume. Individually, diabetes and dyslipidemia were generally associated with poorer neuroperformance and brain imaging outcomes.

Conclusion: Increased vascular comorbidity burden was associated with clinical and imaging markers of MS severity in this large study. Strategies to optimize comorbidity management in people with MS are warranted.

173. Selective Ageusia in Multiple Sclerosis: Tasting Celery but Not the Dip

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Objective: To discuss selective ageusia in multiple sclerosis

Introduction: While generalized ageusia has been described in Multiple Sclerosis (Doty, 2016) (Dhillon, 2018), selective ageusia in this group has not been reported.

Case Study: A 42 year-old right-handed female with past medical history of Multiple Sclerosis and Ameloblastoma, underwent general anesthesia for tumor resection. After surgery, the patient awoke with reduction of smell to 20% of

normal and totally absent taste except for celery. The patient could taste celery on its own, but when she would dunk her celery into ranch or blue cheese dip, it tasted only like celery without any taste of the dip.

Results: Abnormalities in neurological examination: Cranial Nerves (CN): CN II: Ophthalmologic Examination: bilateral pale discs. CN III, IV, VI: Bilateral internuclear ophthalmoplegia. Motor: 4/5. Drift testing: Right abductor digiti minimi sign. Gait: Unstable tandem gait. Cerebellar: Rapid-alternating movements slow on the right. Holmes Rebound Phenomenon: present on the right. Reflexes: 3+ throughout. Hoffman's reflex: present bilaterally. Chemosensory Testing: Brief Smell Identification Test: 4 (anosmia). Retronasal Smell Index: 1 (anosmia). Gustatory Testing: Propylthiouracil Disc Taste Test: 5 (hypogeusia).

Discussion: This individual has true taste and smell loss, which has been described with demyelinating lesions in Multiple Sclerosis involving the central pathway of taste and taste responsive neurons in the anteromedial temporal lobe, amygdala, and olfactory deficits in the frontal lobes (Doty, 2016). Celery under non-pathological conditions has mild flavor and is mostly texturally mediated with perception of flavor. Thus, the loss of smell and taste would only minimally affect the flavor of celery, which is perceived based on the non-chemosensory components of the food, like texture, crunchiness and wetness. The dip on the other hand, with the absence of crunchiness and unique color would not benefit from such secondary sensory input. An alternative possibility is that she has true taste loss due to constriction of the vascular bundle and chorda tympani damage from Crowe-Davis device during oral surgery (Klasser, 2008). Such damage may explain loss of taste. In those with Multiple Sclerosis, query as to perception of food flavor is warranted.

174. Ablation Responsive Palinosmia in Multiple Sclerosis

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Objective: To understand how washing oneself can eliminate persistent smell.

Introduction: Palinosmia is the persistence of the sensation of odor, even after removing the subject from the source (Hirsch, 2009). This is often resistant to alleviation with medical intervention (Wahlstrom, 2015). The elimination of palinosmia with ablution or washing oneself, has not heretofore been described. Such a case is presented.

Case Study: A 74 year-old right-handed female, with past medical history of Sjögren's Syndrome and Multiple Sclerosis, noted that after smelling an odor, the aroma would persist even after leaving the room. This phenomenon would last for up to six hours after initial exposure to the odor. The higher the intensity of the odor, the greater the duration and severity of palinosmia. However, when the patient took a shower, she would experience complete elimination of the persistent smell.

Results: Abnormalities in Neurological Examination: Cranial Nerve (CN) Examination: CN III, IV, VI: Bilateral ptosis. Decreased upward gaze. Motor Examination: Drift Testing: left pronator drift with right cerebellar spooning. Cerebellar Examination: Finger-to-nose dysmetria bilaterally. Holmes Rebound Phenomenon: present on the left. Sensory Examination: Rydel-Seiffer Vibratory Sense: Bilateral upper extremity: 6. Bilateral lower extremity: 0. Chemosensory Testing: Olfactory Testing: Alcohol Sniff Test: 23 (normosmia). Olfactometer Identification Test: left: 14 (hyposmia), right: 14 (hyposmia). Retronasal Olfactory Testing: Retronasal Smell Index: 2 (anosmia). Other: MRI of Brain with and without infusion: multiple hyperintense signals in supratentorial white matter bilaterally. Mild cerebral parenchymal volume loss. Anti-ssb antibodies: positive.

Discussion: There are myriad mechanisms through which ablution may have acted to eliminate palinosmia. The water may have acted to obstruct the nares, blocking air flow and thus eliminating orthonasal olfaction contributing to the palinosmia. Alternatively, as would occur with occluding one end of a manometer, such obstruction may have acted to eliminate retronasal olfaction (Gruss, 2015). Additionally, the water could have acted in the turbinates, inducing the release of an odorant to stimulate the olfactory nerve. This may have acted in a competitive fashion to inhibit any pathological olfactory discharges of palinosmia. Peradventure, the amount of soap present may act as a counter stimulus by competitively inhibiting any persistent false smells (Asiri, 2010). Regardless of mechanism of action, given the low risk of this procedure and potential benefit of eliminating palinosmia, a trial of recurrent ablution in those who suffer from palinosmia is warranted.

175. Leveraging COViMS Registry to Understand the Impact of COVID-19 on Multiple Sclerosis

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Background: Coronavirus disease 2019 (COVID-19) is a disease caused by a novel coronavirus which has resulted in a worldwide pandemic. The majority of people infected have mild disease, however, there is a subgroup of people who develop severe disease, sometimes leading to hospitalization and/or death. Several risk factors have been identified that are associated with worse outcomes in the general population. It

is unclear whether people with multiple sclerosis(MS) are more susceptible to complications of COVID-19 especially in those on certain disease modifying therapies(DMTs). COViMS is a North American clinician registry that is capturing data on outcomes of people with MS and other CNS demyelinating diseases who have developed COVID-19.

Objectives: To describe characteristics of patients in COViMS registry who were hospitalized secondary to COVID-19 and identify risk factors for being hospitalized as well as assess those requiring intensive care unit(ICU) management.

Methods: De-identified data were entered into a secure, web-based registry. Cases were requested from health care providers after at least 7 days of known illness. Data collected includes: demographics;diagnosis;DMTs;pertinent COVID-related data;patient outcomes. Current analyses were restricted to laboratory-positive patients. Data were analyzed using a t-test for continuous variables and Pearson's chi-square or Fisher's Exact tests, as appropriate, for categorical variables.

Results: As of June 2, 2020, 206 laboratory confirmed COVID-19 patients were reported; 78 patients were hospitalized and 17 required ICU;11/17-ventilated. Majority of cohort had relapsing-remitting MS(n=135);41 secondary progressive MS;13 primary progressive MS. Mean(SD) age is 50.1(±13.1) years, 73% female, majority Caucasian(71%; Black/African Americans=23%), and mean disease duration 14.2(±9.6)years. Over 80% of patients were on DMTs at the time of COVID-19 infection. Hospitalized patients were older($p<0.001$), had greater percent of progressive disease($p<0.001$), higher disability levels($p=0.001$), longer disease duration($p=0.002$), more comorbidities (cardiovascular disease[$p=0.008$];chronic lung disease[$p=0.004$];diabetes[$p=0.008$];hypertension[$p<0.001$]; obesity[$p=0.038$]), and active pneumonia($p<0.001$) compared to non-hospitalized patients. Compared to hospitalized patients without ICU needs, those requiring ICU had more comorbidities($p=0.035$), and more deaths(6 to 2,respectively; $p=0.002$). Importantly, there was no significant difference in COVID-19 severity whether patients where on a DMT or not ($p=0.7$) and type of DMT.

Conclusions: Although these data are subject to reporting biases, the impact of COVID-19 on MS appears similar to general population. Our data does not suggest that DMTs increase risk for severe COVID-19 disease course. Data will continue to be collected to confirm this preliminary impression especially since this has relevance to MS treatment guidelines related to COVID-19.

176. Vascular Disease Risk Factors in Multiple Sclerosis (MS) is Associated with Brain Adenosine Triphosphate Abnormalities: Dysmetabolism May Drive MS Disease Progression

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Background: VDRF, such as hyperlipidemia, hypertension, obesity, diabetes, and heart disease, appear to significantly increase the risk of disability progression in MS, however the underlying mechanisms are not well understood.

Objective: To determine if presence of VDRF affects disease progression and brain phosphate metabolism in people with MS.

Methods: This is a 3-year prospective, observational, single-site, study with two arms (MS subjects with and without VDRF). We collect 7T MRI brain data at baseline, 12, 24 and 36 months (V1, V2, V3 and V4 visits, respectively) and clinical and biomarkers data every 6 months. Outcome measures include changes in: 1) high energy phosphate metabolites in cerebral gray matter assessed by ^{31}P 7T MR imaging (MRSI) and 2) brain parenchymal volume, 3) clinical impairment, disability, and quality of life.

Results: We preformed cross-sectional and longitudinal analyses of MRI data (52 V1 and 37 V3 subjects). Mean age/gender was 54.6 years with 71% female) (+VDRF, N=29, mean age 56.3 years, 83% female) and -VDRF, N=23, mean age 52.4 years; 57% female) at baseline. We analyzed a volume of interest in the occipital region for changes in phosphate metabolites (V1 and V3) using 7T MRSI. We observed decrease in Adenosine triphosphate (ATP) to total phosphate signal ratio in +VDRF subjects by 3.3% ($P<0.05$) compared with -VDRF. +VDRF subjects showed a larger reduction in parenchymal volume fraction (0.01544, $P=0.025$) over time (between V1 and V3) compared to -VDRF (0.00423). No significant group differences in temporal changes in phosphate metabolites are seen. Additional analyses are underway.

Conclusion: This is the first study to assess brain metabolism and volume in MS patients with and without VDRF. **+**VDRF MS subjects have significantly reduced brain ATP compared with -VDRF. ATP depletion may reflect mitochondrial dysfunction and contribute to MS disease progression as suggested by the increased brain atrophy in those with VDRF.

177. Progressive Multifocal Leukoencephalopathy Lesion and Brain Parenchymal Segmentation from MRI Using Serial Deep Convolutional Neural Networks

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Background: Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic brain infection caused by the JC virus associated with substantial morbidity and mortality. There are currently no validated automatic methods for quantifying PML lesion burden or brain atrophy on MRI. We assessed whether deep learning techniques can be employed for automated PML brain parenchymal and lesion segmentation using an approach dubbed "JCnet," named after the causative viral agent.

Methods: We performed a retrospective analysis of PML patients evaluated at the NIH Neuroimmunology Clinic. MRI scans were acquired on either a Siemens Skyra or a Philips 3T MRI scanner. For PML brain and lesion segmentation, we implemented a 3D patch-based approach with two consecutive convolutional neural networks (CNNs) with a feature pyramid architecture. The first network extracts PML brain parenchyma from background voxels, whereas the second segments the underlying PML lesion(s). We measured the segmentation accuracy using Dice similarity coefficient (DSC) and absolute volume differences (AVD). We evaluated JCnet against methods designed for normal-appearing brain segmentation, FSL/FMRIB's Automated Segmentation Tool (FAST) and FreeSurfer, as well as multiple sclerosis lesion segmentation, Lesion Segmentation Toolbox (LST) and Lesion-TOpology-preserving Anatomical Segmentation (LTOADS). Comparisons were performed using Wilcoxon signed-ranks test.

Results: A total of 41 PML patients (mean age 55 years, SD 13; 44% female) were included. The cohort was divided into 31 training and 10 testing cases sampled at random. The mean time between PML onset and MRI acquisition was 4.5 months (range 0.6-44.5 months). Using manual delineations as reference, JCnet resulted in a 4% and 64cm^3 absolute improvement in DSC and AVD compared to FAST (p=0.005 and 0.01), and a 6% and 41cm^3 absolute improvement in accuracy compared to FreeSurfer (p=0.005 and p=0.02). This was driven in part by improved segmentation of brain tissue within T1-hypointense PML lesions. For PML lesion segmentation, there was an absolute improvement of 42% and 14cm^3 in DSC and AVD respectively compared to LST, and 53% and 19cm^3 absolute improvements compared to LTOADS (p=0.005 for all lesion comparisons). This was driven by improved sensitivity of supra- and infratentorial PML lesion segmentation.

Conclusions: We developed an end-to-end deep learning method for automated segmentation of PML lesion and brain parenchyma. By tracking quantitative measurements of PML-related MRI changes, this approach provides a window for accurately monitoring PML radiographically and its response to experimental therapies.

178. Brain Functional Connectivity is Related to Leptomeningeal Enhancement in Relapsing-Remitting Multiple Sclerosis: A 7-T MRI Study

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Background and Objective: We have previously shown that leptomeningeal enhancement (LME) is common in relapsing-remitting multiple sclerosis (RRMS) and is linked to gray matter lesions. This study aimed to explore whether LME status is linked to distinct whole-brain functional connectivity (FC) patterns in RRMS, and investigate relationships between FC metrics and cortical and thalamic lesions (CLs and TLs).

Methods: Twenty-seven RRMS patients (age mean±SD, 46.0±0.9 years; 19 women) and 13 age- and sex-matched healthy controls (HCs) participated in this single-site study. All subjects underwent 7-T MRI including pre- and post-gadolinium-enhanced 3D MP2RAGE (magnetization-prepared 2 rapid acquisition gradient-echoes), 3D fluid-attenuated inversion-recovery (FLAIR), and resting-state functional MRI (rs-fMRI). LME status, CLs, TLs, and white matter (WM) lesions were expert-quantified. Region-of-interest-based whole-brain FC analysis was performed to compare intrinsic FC patterns between groups adjusting for age, sex, and WM lesion burden. Wilcoxon rank-sum, Fisher's exact test, Spearman correlations, and analysis of covariance (ANCOVA) were performed for statistical analysis.

Results: 19/27 (70.4%) RRMS patients and 1/13 (7.7%) HCs were LME+. Post-hoc analyses of ANCOVA demonstrated that, compared to HCs, LME- patients showed increased FC between the right Heschl's gyrus (HG) and right thalamic ventral lateral nucleus (Thal_VL), and between the right HG and left anterior parahippocampal gyrus (aPaHC), but showed decreased FC between the right lingual gyrus (LG) and left thalamic mediodorsal medial magnocellular nucleus (Thal_MDm). However, compared to HCs, LME+ patients showed decreased FC between the left thalamic medial geniculate nucleus (Thal_MGN) and bilateral Thal_MDm, and between the right occipital fusiform gyrus (OFusG) and right pallidum. Additionally, in LME+ patients, the volume of CLs and TLs were inversely correlated with the FC between the right HG and left aPaHC (Rs = -0.55, p = 0.017; Rs = -0.51, p = 0.027, respectively).

Conclusions: These results reveal that leptomeningeal involvement in RRMS is associated with altered FC in the brain, in part due to the known association between LME and cortical/thalamic damage. The altered FC patterns displayed in patients with different LME status may indicate a distinct neural mechanism in MS progression, suggesting that LME status may provide an early indicator of disease severity in MS.

179. Delayed-Onset Demyelinating Lesions after Radiation Injury: A MS Mimic

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Objective: The 2017 McDonald's criteria suggests a diagnosis of multiple sclerosis (MS) when clinical symptoms and/or neuroimaging favor dissemination in space and time. However, it's sensitivity in distinguishing MS from other etiologies with similar presentations remains low (Brownlee et al., Lancet 2017). Here, we detail clinical, laboratory, and neuroimaging findings from a patient whose presentation, despite meeting McDonald's criteria, is more indicative of continuing sequelae from remote radiation injury.

Design/Methods: This is a case report utilizing retrospective data from electronic medical records. The patient and his family consented to the distribution of all presented case findings in accordance with guidelines from University of California.

Results: Our 46-year-old male Caucasian engineer was in good health with no significant past medical history until a work-related technical malfunction 8 years ago exposed him to extreme levels of multi-frequency microwave radiation. Immediately post exposure, he developed nonspecific eye, joint, muscle and stomach pain, which resolved after conservative management. MRI brain with and without contrast at the time was unremarkable. Four years later, the patient presented with right hand weakness and numbness that only partially improved after anterior cervical discectomy and fusion of C4-C7. Six years after exposure, he developed new-onset left arm and hand weakness. Repeat MRI brain now showed several white matter lesions concerning for demyelinating disease. His presentation fulfilled McDonald's criteria, though post-radiation injury, infectious etiologies, other autoimmune disorders like neurosarcoidosis, and paraneoplastic syndromes remained in the differential. Further investigation revealed negative ANA, SSA/SSB, ANCA, anti-myeloperoxidase, HIV, ACE, CRP. Lumbar puncture revealed normal glucose, protein, no oligoclonal bands and negative infectious studies. A trial of first-line MS medications was refused. He returned to clinic eight years after radiation exposure with burning in stomach, leg weakness, decreased mental clarity, difficulty sleeping and excessive irritability. Repeat MRI demonstrated increasing number of scattered cerebral white matter hyperintense lesions. Interval pan-CT scans now showed nodules in the kidney and bilateral lungs.

Discussion: Our case report details over 8 years of clinical and neuroimaging evidence to support ongoing demyelination in the setting of remote radiation exposure. We present a systematic walkthrough of the multiple etiologies associated with demyelinating lesions to aid neurologists and other practitioners in formulating relevant differentials for their patients. Continued investigations like this will promote targeting of therapies to each patient's unique pathophysiology and minimize the harm from inappropriate treatments.

180. Tumefactive Multiple Sclerosis (TMS): A Case Series of This Uncommon Yet Challenging Variant of MS

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Background: Tumefactive MS (TMS) is a rare variant of multiple sclerosis that poses a diagnostic and a therapeutic challenge due to its close resemblance to central nervous neoplasms on MRI. TMS is defined as acute large >2 cm, tumor like demyelinating lesion in the CNS that may occur with surrounding edema, mass effect and ring enhancement. Some of the known mimickers are CNS lymphoma, metastasis, primary brain tumor such as glioblastoma, brain abscesses. The prevalence of TMS is estimated to be 1-3/1000 MS cases. There are also reported cases of drug induced TMS cases especially with fingolimod and natalizumab therapy. We report the occurrence of TMS at our institution.

Methods: The list of patients was obtained using multiple sclerosis, optic neuritis as the search criteria in electronic medical record system at our institution. We retrospectively reviewed the chart of the patients and collected data on demographic, ethnicity, presenting signs and symptoms, imaging modalities, cerebrospinal fluid analysis results, disease progression. After reviewing the charts, we isolated the patients with TMS from the group and summarized the cases.

Results: Out of 323 patients reviewed with MS or possible MS, 7 carried a diagnosis of TMS. The age range of these patients were 19 to 62 years old with 4 females and 3 males. Five patients were Caucasian and 2 were Hispanic. Out of seven patients, 6 were newly diagnosed MS following biopsy of the lesion. Weakness was predominant presenting symptom in 6/7 patients. Oligoclonal bands in CSF were present in only 3/7 and absent in 4/7 patients. The histological findings in 3 patients who underwent biopsy demonstrated include reactive gliosis and inflammatory cells predominantly macrophages and lymphocytes while 1 patient showed hypercellular brain tissue with perineuronal satellosis. Four of these patients were managed with Glatiramer acetate, 2 on dimethyl fumarate and 1 on beta interferon with 0-2 clinical flare ups on subsequent (mean= 3.4) years.

Conclusion: TMS is more common than previously reported prevalence among MS patient population. The demographic of the patients in this case series is no different than patients with relapsing remitting multiple sclerosis (RRMS). However, based on our experience, the patients with TMS do respond to disease modifying agents such as Glatiramer acetate and Dimethyl fumarate with similar progression as of RRMS.

181. Radiologically Isolated Syndrome vs. Multiple Sclerosis; Case Report with Review of the Literature

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Multiple sclerosis is an unpredictable inflammatory neurological disorder that can lead to severe disability in some, while others are left asymptomatic. A diagnosis of multiple sclerosis calls for a dissemination in time and in space. Radiologically Isolated Syndrome (RIS) is a clinical phenomenon that occurs when an individual has visible central nervous system (CNS) white matter disease as seen on MRI; yet, has little-to-no clinical significance. RIS classically demonstrates dissemination in space but not time. For individuals with Radiologically Isolated Syndrome, incidental white matter

lesions are noted following an MRI for typically inapplicable to multiple sclerosis. In this case, we report a clinical case initially suspicious of infectious etiology, then RIS, and later confirmed as MS with review the current literature of RIS. An important aspect of this case is in consideration for oligoclonal bands - in that, it may be used as a marker for dissemination in time.

K-591. **Preferential correlations between thalamic subregions and neuroperformance measures in progressive multiple sclerosis.**

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Background: Thalamic volume is associated with physical disability and cognitive impairment.

Objectives: To examine the relationship between thalamic subregional volume and neuroperformance measures in patients with progressive MS.

Methods: We correlated clinical neuroperformance and MRI measures in 291 subjects with progressive MS: 136 primary progressive (PP), 123 secondary progressive (123), and 32 unknown progressive type] from the SPRINT-MS baseline dataset. Multiple Automatically Generated Templates (MAGeT) brain segmentation was used to obtain volumes of thalamic subregions.

Results: Overall, thalamic volume correlated with 9-hole peg test (9-HPT) in the dominant hand (Spearman's rho -0.22, p = 0.0001) with lateral posterior nucleus having the highest correlation (rho = -0.12, p = 0.04) of the subregions. Thalamic volume in PP correlated with 9-HPT better than SP (rho = -0.30 vs. -0.19). Of the thalamic subregions, the pulvinar in PP (rho = -0.25, p = 0.003) correlated best (none in SP). Overall, Symbol Digit Modality Test (SDMT) correlated with thalamic volume (rho = 0.23, p < 0.0001) and the pulvinar nuclei best (rho = 0.27, p < 0.0001). Thalamic volume correlated with SDMT in SP more than PP (rho = 0.37 vs 0.21). The pulvinar correlated with SDMT best in PP (rho = 0.30, p < 0.001) and the dorsomedial nucleus in SP (rho = 0.41, p < 0.0001). Multivariable linear modeling of the relationship between neuroperformance measures and longitudinal thalamic subregional changes at 8 years (n = 214) will be provided.

Conclusions: Thalamic subregions correlated preferentially with manual dexterity (9-HPT) and cognitive impairment (SDMT) and differed among PP and SP disease courses. These results implicate differences in neurodegenerative patterns with physical and cognitive impairment between progressive MS courses.

Neurocritical Care

316. Dynamic Changes in Brain and Body Variables Predict Recovery in Acute Traumatic Brain Injury Coma

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The dynamic interaction of brain and body functions in the regulation of homeostasis is an emerging issue in the study of complex biological systems *(Buchman TG, Nature, 2002) (Bashan A, Nature Communications, 2012)*. Acute brain injury coma patients represent a clinical challenge in terms of outcome prediction and allocation of resources. Most predictive biological variables have been measured at a single time point, and, until recently, organ-specific variables (e. g. Glasgow Coma Scale, GCS, blood pressure, and inflammation) have been considered separately in the Intensive Care Unit (ICU) *(Asada T, Critical Care, 2019)*. The aim of this project was to apply, for the first time, a time-dependent analysis of brain and body variables and their interaction to coma. This retrospective study involved a cohort of acute coma patients (n=21) admitted to the Neuro-ICU after traumatic brain injury (TBI). Several systemic parameters were measured longitudinally along with GCS. The cohort was divided into a favorable (F, n=15) or unfavorable (U, n=6) outcome, based on the Glasgow Outcome Scale Extended (GOSE). A repeated ANOVA between F and U patients examined mean and SD difference across different parameters, in the presence/absence of sedation. The relationship between variables and groups of variables was assessed by linear regression. Finally, we identified different awakening patterns in F patients. We found that variables in different domains: brain, cardiovascular, inflammation/immune system, and gastrointestinal distinguished between F and U groups. For example, a more unstable pupillary size was associated with U outcome, and this was evident already under sedation. Higher levels of C-reactive protein characterized the U group in the first days of coma. The platelet count increased in the F group after the withdrawal of sedation and was overall higher than in the U group. Gastric emptying occurred earlier and more frequently in the F group. The correlation between variables of different systems varied depending on sedation and outcome. In our explorative analysis, even if limited by the complex ICU setting, brain and body variables changed over time and distinguished different levels of consciousness after the end of sedation. These findings show for the first time multi-systems interaction of brain and body variables in coma recovery. We speculate that this interaction reflects the re-synchronization of brain and body rhythms in the recovery from coma.

317. MRI Findings in Acute Hyperammonemic Encephalopathy Secondary to Acetaminophen Toxicity

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Distinct MRI changes of acute hepatic encephalopathy have been described which may be misinterpreted given their resemblance to hypoxic-ischemic injury imaging changes as well as their limited description in the neurologic literature. We present a case of acetaminophen toxicity resulting in acute fulminant liver failure and acute hyperammonemic

encephalopathy and acute MRI changes in the absence of a hypoxic-ischemic event. 43-year-old woman presented with abdominal pain and chest pain for three days after ingestion of 50 tablets of 650 mg acetaminophen tablets. Initial presentation, her aspartate transaminase level was more than 7000 U/L, alanine transaminase was 4300 U/L, alkaline phosphatase was 101 U/L, INR of 6.5 and ammonia of 130 micromol/L. On day one of presentation, her mental status was normal. She was started with N-acetylcysteine and in spite of this treatment, her mental status declined within few hours to days and she was intubated. On day four, her neurological exam was suggestive of she opens eyes to noxious stimuli and not following commands. Oculocephalic, corneal and gag reflexes were intact. Extension of bilateral upper extremities and triple flexion of lower extremities with noxious stimuli. CT head has shown early thickening of the gyri in the frontal lobes. MRI brain has shown diffuse restricted diffusion involving the cerebral cortices and corticospinal tracts of the posterior limbs of the internal capsule. Ammonia level was 184 micromol/L. EEG consistent with profound diffuse encephalopathy. History or hospital course was not suggestive of hypoxia or hypotension or hypoglycemia or pulseless electrical activity. She was not a candidate for liver transplant because she was thought to have poor prognosis. Over the course of a month, she had significantly improved with mental status, liver function with continued N-acetylcysteine treatment. Symptoms of patients with acute hyperammonemic encephalopathy include sudden onset of drowsiness and seizures. Untreated hyperammonemia can lead to permanent brain injury. In the clinical setting of hyperammonemia, a pattern of bilateral symmetric involvement of insula, cingulate cortex, diffuse cerebral cortex, and dorsomedial bilateral thalami manifesting predominately on MRI as restricted diffusion, should alert the clinician to the possibility of hyperammonemic encephalopathy, especially in the absence of a hypoxic-ischemic event. It is very important to differentiate with hypoxic ischemic encephalopthy (HIE) because acute hyperammonemic encephalopathy is reversible if early diagnosis and proper treatment is done but HIE is irreversible.

318. A New Normal after Severe Acute Brain Injury: An Observational Cohort Using a Sequential Explanatory Design

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Background: Severe acute brain injury (SABI) is a major cause of disability and mortality that is challenged early on by prognostic uncertainty. As patients lack decision-making capacity, their family members are called to make treatment decisions based on patient's presumed goals of care (GOC). This study aims to (1) assess patient's presumed GOC in the intensive care unit (ICU); (2) explore adaptation in a subgroup of survivors whose outcome was worse than what they might have found acceptable, and their families.

Methods: Participants were family of patients with SABI who had been in our Neuro-ICU for >2 days and had a Glasgow Coma Scale <12. We developed a SABI-specific GOC questionnaire and asked what level of functional or cognitive recovery their loved one would find acceptable at 6 months. We assessed actual outcome at 6 months through family survey and chart review. Families of patients whose 6-month outcome was worse than their GOC (what had been initially considered acceptable), were invited for semi-structured interviews until theoretical saturation, using qualitative content analysis.

Findings: In terms of cognitive recovery, most families (150/184 = 82%) set their loved one's GOC at "able to think and communicate" or better. For physical recovery, most families set their loved one's GOC at independence (67%). Over one third (39%) of patients died in the hospital. At 6 months, outcome was known for 175 patients. One third of survivors (n=34, 33%) was able to think and communicate, 14% were functionally independent and 4% died in the post-acute setting. Among survivors whose family member had drawn the line for cognitive recovery at "able to think and communicate", 53 (60%) survived below that level. Qualitative analysis revealed 2 key themes: (1) Families describe the process of **adaptation to a new normal** that includes grieving their past as they continue to hope for its recovery; (2) as families are faced with **ongoing treatment decisions**, they call for more guidance from the neurological field. Both themes are challenged by ongoing uncertainty.

Interpretation: Almost two thirds of survivors remained at a state they might not have found acceptable 6 months after SABI. Survivors and their families call for more support and guidance from the neurological field as they adapt to a new normal and struggle with persistent uncertainty.

319. Models Integrating Epileptiform Abnormalities, TCD, and Clinical Variables Improve DCI Prediction after SAH

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Introduction: Delayed cerebral ischemia (DCI) is the leading complication of subarachnoid hemorrhage (SAH). Transcranial doppler ultrasound (TCD) remains the standard of care for DCI monitoring despite its variable sensitivity/specificity and ability to only detect vasospasm. With growing evidence for other contributing mechanisms to DCI, supplementary diagnostic tools are needed. Continuous EEG, including epileptiform abnormalities (Kim 2017, Rosenthal 2018), is a promising tool to identify patients with increased DCI risk. We hypothesize that combining these complimentary diagnostic modalities improves DCI prediction.

Methods: We assessed 107 patients with moderate-severe SAH (2011-2015) who had both TCD and EEG monitoring during hospitalization. Middle cerebral artery (MCA) peak systolic velocities (PSV) and the presence or absence of epileptiform abnormalities (EA), defined as seizures, epileptiform discharges, and rhythmic/periodic activity, were recorded daily. Linear imputation was used for missing MCA data, and TCD and EEG data were dropped out after DCI occurs. Clinical demographics, including Hunt Hess, were collected on admission and via retrospective chart review. Logistic regressions were used to identify significant covariates of EA and TCD to predict DCI. Forward selection was then used to select for the best adjusted multivariate model with these predictors. Leave-one-out cross validation was used to evaluate model sensitivity and specificity.

Results: The independent predictors of DCI were presence of high MCA PSV, defined as PSV>200cm/s, ($p=0.04$, sensitivity=0.27, specificity=0.89) and presence of EA ($p<0.01$, sensitivity=0.66, specificity=0.62) on or before day 3. Combining both parameters improved DCI prediction ($p<0.05$, sensitivity=0.76, specificity=0.57) compared to either alone. Univariate logistic regression models found increased Hunt-Hess score at admission ($p<0.01$) and clipping of aneurysm ($p=0.02$) to be associated with increased risk of DCI. Adjusting for these clinical predictors of DCI in the combined TCD and EEG model further improved DCI prediction, and the best performing model included aneurysm treatment, Hunt-Hess score, presence of EA on or before day 3, and high MCA PSV on or before day 3 ($p<0.05$, sensitivity=0.91, specificity=0.71).

Conclusion: Our data suggest that the combination of TCD, EA and clinical variables improves DCI prediction.

320. Characterizing Blunt Cerebrovascular Injuries and Stroke: A Single Center Retrospective Study

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Introduction: Ischemic stroke is a significant consequence of blunt traumatic cerebrovascular injuries (BCVI). However, due to frequent concomitant polytrauma as well as traumatic brain injury, an accurate diagnosis of BCVI may be delayed and effective treatment remains obscure with studies reporting a risk of stroke of 10%. Further, BCVI has rarely been investigated by the neurology and stroke communities. We were interested in identifying the patterns of injuries and timelines of neurologic consultation at our center, and their relation to stroke risk and diagnosis to inform potential therapeutic strategies.

Methods: A trauma registry database from a Level 1 Trauma Center was surveyed to identify patients admitted with a BCVI from the years 2016-2019. The descriptive analysis included the following components: demographic information, diagnostic modalities, vessel injury characterization, other injuries, neurology consultation, interventions, and outcomes.

Results: A total of 40 patients (mean age: 44.1 years old; 80% male) were identified. Motor vehicle collision was the most common cause of injury (55%) and most patients were registered as a level 1 trauma (63%). Neurology was consulted for 43% of patients, an average of four days following admission. Eighteen patients had a carotid artery injury (33.3% stroke) and twenty-seven patients had a vertebral artery injury (11% stroke). Vertebral artery injuries were more frequently accompanied by cervical spine fractures compared to carotid injuries (67% vs. 17%), but thirteen patients (32%) with BCVI had no cervical fracture. A total of 9 patients (23%) had a stroke with half occurring within two days of admission. No patients received intravenous alteplase or mechanical thrombectomy, although two underwent non-emergent carotid stenting for secondary prevention. While 80% of all patients received an anti-platelet, anti-coagulant agent, or both, antithrombotic medication was not started on half of all BCVI patients until day 2. A total of eight patients died, five of whom had strokes.

Conclusions: Stroke was a frequent complication of BCVI in our population. However, none received emergent treatment, less than half had a neurology consultation, and the initiation of antithrombotic medications was often delayed. Early recognition of carotid and vertebral injury, neurologic consultation, and timely initiation of antithrombotic therapy may represent an opportunity to reduce the burden of stroke from BCVI.

321. Effects of HIV on T1w/T2w Cortical Myelin

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Myelin maps of the cortex, estimated from the ratio of T1w and T2w MRI anatomical scans were compared between 183 people living with HIV (PLWH) and 153 healthy controls (HC). PLWH were older ($p<0.001$) and with higher percentage of male participants ($p<0.001$). The groups did not differ significantly with respect to composition of ethnicity ($p=0.122$). The HC group on average had larger number of years of education ($p=0.019$). The median nadir and recent CD4 values for PLWH were 205 and 453 cells/mm3 respectively. To account for atrophy cortical thickness was estimated from the anatomical scans and along with age was used as a covariate in the linear models. HC had significantly higher levels of whole cortex myelin ($p=0.0034$). No significant effect ($p>0.15$) on the association of myelin with age was observed by viral status group. The association with age was significant, with decreasing slopes for both groups ($p<0.01$). The HC group showed a trend of decreasing myelin with improving neuropsychological Z-score (NPZ-4) ($p=0.047$), while myelin for PLWH had no association with cognitive performance ($p=0.894$) and nadir and recent CD4 cell counts ($p<0.001$). The HC group, had higher myelin in the insula, inferior temporal, precuneus, posterior and caudal anterior cingulate, medial orbito-frontal ($p<0.01$) as well as in the rostral middle frontal, supramarginal, inferior parietal, isthmus cingulate, fusiform ($p<0.05$). An exception was the postcentral gyrus where PLWH had slightly higher myelin ($p=0.42$). That ROI had the smallest average thickness

among the significant ROIs. The posterior cingulate, as a representative ROI had similar relationships of myelin to age, NPZ-4 and nadir CD4 as the whole cortex, but there was an increase in myelin with higher recent CD4 count (p=0.021). The observed reduction of myelin in the whole cortex and in eleven ROIs across age (19-82 yo) might be viewed as one of the possible causes for the continued manifestation of HAND in virologically suppressed PLWH. The eleven significant ROIs are associated with executive function, memory and sensory processing. HAART seems to be stabilizing the myelin decrease, but doesn't appear to lead to full recovery of its maintenance. Thickness perhaps can be viewed as a proxy for density, with smaller cortical thickness (the postcentral gyrus) representing denser tissue and elevated T1w/T2w ratio. Further analyses should include the demonstrated reduction of cortical myelin in PLWH, relating it to other neuroimaging and neuropsychological studies of the HIV seropositive population.

322. Comparison of Optic Nerve Sheath Diameter as a Non Invasive Measurement of Raised Intracranial Pressure with Ventricular Catheter in 51 Patients - An Exclusive Neurocritical Care Institutional Experience

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Background: Raised intracranial pressure (ICP) is a known association with traumatic brain injury, acute stroke, meningitis and brain tumors. Bedside identification may be difficult and reliability on imaging studies further delay diagnosis. Examination of the optic nerve sheath by bedside ultrasound allows detection of changes in diameter(ONSD) which may predict intracranial hypertension.

Objectives: Comparing the measurements of ONSD obtained by using bedside ultrasound to invasive ICP for detecting raised ICP in patients admitted to Neuro Intensive care unit(NICU) with predominantly intracranial bleeds.

Methods: A prospective, observational study on 51 adult patients who were admitted in NICU with TBI and strokes presumably having elevated intracranial pressure. All patients were examined in supine position using a 10 MHz ultrasonographic probe on the closed eyelids, a single ONSD measured 3 mm behind the globe in each eye. A mean binocular ONSD >4.6 mm in female and 4.8 mm in male were taken as cut-off values. ICP monitoring was done by standard external ventricular drain (EVD) placement. This was connected to the pressure transducer for continuous ICP monitoring. ONSD and ICP was measured every 4 hrly for 24 hrs.

Results: Mean age of the study population was 68.29. It was observed that 52.9% patients had GCS between 9 - 13 and 47.1 % had GCS between 3 - 8. The Mean Pre EVD ONSD and Post EVD ONSD at serial measurements were significantly more in the patients with GCS between 3 - 8 compared to patients with GCS between 9 -13, $p < 0.05$. The mean ICP at 0 and 4 hrs was observed to be significantly higher in patients with GCS between 3 - 8 compared to patients with GCS between 9- 13, $p < 0.05$. There was a significant and positive correlation between Pre EVD ONSD and ICP and post EVD ONSD with serial ICP measurements.

Conclusion: The use of bedside ocular USG in measuring ONSD was comparable to EVD in detecting raised ICP. It has the advantages of being a non-invasive, bedside test, which can be repeated multiple times for re-evaluation. Large number and varied central nervous system pathologies are recommended in order to standardize the measurement of ONSD with invasive ICP to detect raised ICP.

323. Neurologic Consequences of Covid-19 Coronavirus Infection Correspond to ACE2 Receptor At1 Proinflammatory and Procoagulant Responses

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Objective: What is the pathogenic basis of COVID-19 CNS symptoms and signs?

Background: There are six previously described strains of human coronaviruses, each primarily associated with respiratory conditions ranging from the common cold to pneumonia and bronchiolitis. They are designated OC43, 229E, NL63, HKU1, SARS and MERS. Most recently, SARS-2 (COVID-19) appeared. While the majority of coronavirus infections have been limited, SARS was more widespread and caused significant mortality in some. SARS-2 (COVID-19), with greater infection efficiency, rapidly eclipsed the SARS. SARS, SARS2 and NL63 all use the angiotensin converting enzyme, ACE2 receptor, to enter the cell, but SARS-2 has posed most serious challenges, reflecting the rapid onset and broad spectrum of symptoms and signs of COVID-19 infection.

Design/Methods: This report surveys autopsy findings in COVID-19 patients, and unique features of clinical presentation. The focus was on comparison of pathology localization with ACE2 receptor distribution.

Results: Tissue pathology was most severe where ACE2 receptor localization is greatest. This includes the lung, the heart, the kidney and the brain as well as blood vessels. In addition to direct cytopathic and cytolytic effects of COVID-19, the proinflammatory impact triggering a cytokine storm causes tissue destruction in the lung. Procoagulant activity initiating clots, causes deep vein thrombosis, pulmonary embolism and vascular changes in distal limbs, as well as in the brain causing strokes.

Conclusions: The response to the SARS2-ACE2 receptor interaction in COVID-19 is far more intense than in SARS or NL63. The overall increased severity and higher mortality in older individuals and selected racial backgrounds as compared to previously healthy younger individuals requires explanation. Careful analysis of predisposing factors, whether genetic variation in receptor expression, concomitant medication use or concurrent illness is needed. Coronavirus tissue tropism in mouse models implicates host factors, including virus receptor distribution and expression, as well as host immune responses. COVID-19 morbidity appears closely associated with ACE2 receptor modulation and subsequent inflammatory/coagulant responses. The rapid cadence of

these tissue responses in COVID-19 requires early awareness of the virus and early intervention in blocking its effects.

324. Intracerebral Hemorrhage and Clinical Outcome on Low Field, Portable, Point-of-Care Magnetic Resonance Imaging

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Background and Aims: Portable, low-field MRI allows for neuroimaging at the point-of-care (POC). We aim to assess the accuracy of hematoma volume measurements in low-field, POC MRI and its relationship with clinical outcome in patients with intracerebral hemorrhage (ICH).

Methods: We studied 27 patients (11 females; ages 21-82 years) with ICH. T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) exams were obtained on a 64mT, portable MRI system. Three raters used the ABC/2 method to measure hematoma volumes on POC exams and the closest standard-of-care (SOC) exam (8 CT; 16 1.5/3T MRI) within 36 hours. Intra-class correlation coefficients (ICC) were computed to assess: (1) inter-rater agreement of measurements and (2) accuracy of POC volumes compared to SOC volumes. POC volumes were correlated against National Institutes of Health Stroke Scale (NIHSS) scores at the time of scan, length of hospital stays, and discharge functional outcomes (modified Rankin Score).

Results: POC MRI exams were performed within 3.4±3.2 days of symptom onset. Three patients were excluded from further analysis due to motion degradation of images. For the remaining 24 patients, hematoma volumes ranged from 0.5cc to 30cc (median=8.4cc). There was strong inter-rater agreement in measurements for POC T2W (ICC=0.99, p<0.0001), POC FLAIR (ICC=0.96, p<0.0001), and SOC (ICC=0.94, p<0.0001) exams. Average POC volumes (T2W and FLAIR) and average SOC volumes (T2W, FLAIR, and CT) were significantly correlated (ICC=0.88, p<0.0001). There were significant correlations between POC T2W and SOC T2W volumes (ICC=0.94, p<0.01), POC FLAIR and SOC FLAIR volumes (ICC=0.76, p<0.01), and average POC and SOC CT volumes (ICC=0.87, p<0.01). POC T2W volumes significantly correlated with discharge clinical outcome (r=0.55, p<0.01), length of stay (r=0.56, p<0.01), and NIHSS scores at time of scan (r=0.74, p<0.0001). POC FLAIR volumes significantly correlated with discharge clinical outcome (r=0.61, p<0.01) and length of stay (r=0.46, p<0.05).

Conclusion: POC MRI volume measurements significantly correlated with SOC volume measurements, and there was a significant association between size of hemorrhage on POC MRI images and discharge clinical outcome. Further work is needed to validate these findings and to demonstrate the role of POC MRI in predicting long-term outcome after ICH.

325. Quetiapine Use in the Neurocritical Care Setting

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Delirium is an acute neuropsychiatric disorder characterized by a disruption of cognition, orientation, and consciousness often in a fluctuating pattern that occurs frequently in critically ill patients. It is estimated that about 28% of patients over the age of 65 in the ICU will develop acute delirium. It is a disorder that may be over-looked, while addressing other acute and critical care needs in patients; however, individuals with delirium during an inpatient say are at higher mortality risk. While there are conflicting evidence suggesting the utility of anti-psychotic medications in the ICU setting, anti-psychotic medications are occasionally elected for in the setting of acute hyperactive delirium as a safety measure for patients and medical personnel. In this article, we review current literature of quetiapine in the ICU setting.

326. Peri-Arrest Characteristics and Outcomes in Overdose-Related Cardiac Arrest

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Introduction: Research on overdose-related cardiac arrest (ODCA) is limited, and a better understanding of the impact of peri-ODCA factors on neurological prognostication is needed. We sought to compare baseline and peri-arrest characteristics of ODCA patients with non-ODCA to assist in prognostication of this population.

Methods: From 114 consecutive patients presenting between June 2014 and October 2018 after cardiac arrest at a university-affiliated safety net hospital using the Multimodal Outcome CHAracterization in Comatose Cardiac Arrest registry, we abstracted baseline characteristics, peri-arrest factors, and discharge outcomes. Poor outcome was defined as Cerebral Performance Category (CPC) score 3-5 or modified Rankin Scale (mRS) score 4-6. We compared the characteristics and outcomes between ODCA and non-ODCA cohorts with unpaired t-tests, Chi-square or Fisher's exact tests, and logistic regression using SPSS.

Results: Of the 114 cardiac arrest patients, 54 (47%) were ODCA, with 89% (48/54) of ODCA related to opiate usage. ODCA patients were younger (45 vs 60 years, p<0.0001), had more CA in the field (93% vs 77%, p=0.021), more unwitnessed arrests (70% vs 40%, p<0.0001), longer time to ROSC (15 vs. 5 min, p=0.011), and were more likely to become brain dead (44% vs. 27%, p=0.047). ODCA status was predictive of higher in-hospital death when controlling for age (aOR 3.26 [1.16 - 9.17], p=0.025). Adjusted for age and ODCA status, in-hospital death was positively associated with initial non-shockable rhythms (aOR 11.8 [3.56 - 39.07], p<0.0001). ODCA patients had higher rates of poor

CPC scores (2% vs. 14%, p=0.026), and less favorable dispositions when surviving to discharge (50% vs. 90% to home or acute rehabilitation, p=0.024).

Conclusion: The majority of patients who suffered ODCA were from opiate use. The odds of in-hospital death after cardiac arrest was > 3 times greater in ODCA patients. Among survivors, ODCA patients required higher levels of care on discharge. The peri-arrest course of ODCA patients was significantly worse than that of the non-ODCA cohort, possibly contributing to worse outcomes and survival.

327. Can Lateralized Periodic Discharges Serve as a Prognostic Tool in Soporific Acute Hyperammonemic Encephalopathy (AHE)?

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Objective: We present an interesting case with LPDs (Lateralized Periodic discharges) secondary to severe hyperammonemia refractory to multiple Anti-Epileptic Drugs (AEDs) resulting in poor outcome.

Background: Hepatic Encephalopathy (HE) in cirrhotics cause slowing on EEG while status epilepticus is a rare manifestation.

Case: A 66-year-old female with a medical history of Non-Alcoholic Steatohepatitis (NASH) cirrhosis complicated by hepatorenal syndrome presented to the emergency department with progressive lethargy. On examination, she was unresponsive to verbal or painful stimuli but brain stem reflexes were intact. Laboratory findings were significant for leukocytosis upto 17,000/μL , total bilirubin of 3.7 mg/dL, Alkaline Phosphatase of 535 U/L and Ammonia level of 1,519 μmol/L. The patient was intubated for airway protection. On day 2, she had myoclonus-like twitching of her face. Continuous Video Electroencephalogram (VEEG) demonstrated lateralized periodic discharges (LPDs) over the left and right posterior regions with a background of severe encephalopathy. MRI of the brain without contrast showed restricted diffusion involving the cerebral cortex bilaterally with a similar distribution on Fluid Attenuated Inversion Recovery (FLAIR) without Apparent Diffusion Coefficient (ADC) correlate.

Results: Despite treatment with multiple AEDs, correction of her hyperammonemia and other metabolic derangement's, the patient continued to have LPDs with no neurological improvement. Due to multiple medical complications during her hospital stay, the family decided to withdraw further care and she expired thereafter.

Conclusions: Hyperammonemia is known to cause neuronal dysfunction prominent in the cortex and in basal ganglia. Classical EEG findings include diffuse slowing with intermittent triphasic waves. Hyperammonemia causing LPDs are an uncommon finding though there are reported cases of such patients noted to develop status epilepticus with an associated poor outcome. Our case hypothesizes the possibility that underlying LPDs in severe hyperammonemia could serve as a potential marker for poor prognosis. Further studies are needed to better correlate an underlying association

328. Percutaneous Coronary Intervention Complicated by Anterior Spinal Cord Infarction

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Introduction: Anterior spinal cord infarction is a rare form of ischemic stroke that can be debilitating for patients. Known causes include embolism, atherosclerosis, systemic hypotension, trauma, vasculitis, vasculature compression, vertebral artery dissection, and iatrogenic spinal cord injury. Anterior spinal cord infarction accounts for approximately 0.3% -1.0% of strokes. We report a case of a 67-year-old man with severe CAD presenting with STEMI who underwent a PCI requiring Impella support complicated by anterior spinal cord infarction.

Case: After the procedure, overnight, the patient developed mottling (suspected livedo reticularis) and briefly required vasopressor support because of hypotension. He woke up with lower extremity weakness and numbness bilaterally, and bowel and urinary incontinence. He was AO x 3 and without any changes in mental status. On examination, the patient had normal cranial nerve findings, sensations to all modalities were intact in upper extremities but absent below the T6 dermatome except for vibratory and proprioceptive sensations. Reflexes were 2+ in brachioradialis and patellar bilaterally with mute Babinski. Rectal tone was also absent. MRI Spine performed immediately afterwards did not show any abnormalities but 2 days later showed extensive T2 intramedullary hyperintensity in the middle thoracic spinal cord extending caudally to conus medullaris along with restricted diffusion, concerning for spinal cord infarction. Subsequently, he had lumbar drain placed to improve spinal cord perfusion by draining 5-10 ml CSF every hour.

Discussion: Thromboembolic strokes involving the brain are known complications of PCI and livedo reticularis is a sign of embolism. The spinal cord is supplied by a single anterior and paired posterior spinal arteries. From T5 to L2 level, the anterior spinal artery is supplied by the artery of Adamkiewicz which is prone to watershed infarction. We hypothesize that our patient had a spinal cord infarction likely from embolism secondary to PCI worsened by severe hypotension. A combination of embolism and severe hypotension shows that multiple etiologies may worsened outcomes. High risk patients include those who have CAD, PAD, age over 60, and iliac artery catheterization that may dislodge a plaque causing embolism. Management involves adequate blood volume resuscitation and perfusion of spinal vasculature during and after PCI. CSF drainage should also be considered. A rehabilitation program may restore some function back to the lower extremities.

K-577. Determinants Of Functional Brain Connectivity After Subarachnoid Hemorrhage

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Aneurysmal subarachnoid hemorrhage (SAH) leads to significant long-term cognitive deficits, which can be associated with alterations in resting state functional connectivity

(RSFC). However, modalities such as fMRI—which is commonly used to assess RSFC in humans—have practical limitations in small animals. Therefore, we used non-invasive optical intrinsic signal imaging to determine the effect of SAH on RSFC in mice up to 3-months after prechiasmatic blood injection. We assessed Morris water maze (MWM), open field test (OFT), Y-maze, and rotarod performance from approximately 2-weeks to 3-months after SAH. Compared to sham, we found that SAH reduced motor, retrosplenial, and visual seed-based connectivity indices. These deficits persisted in retrosplenial and visual cortex seeds at 3-months. Seed-to-seed analysis confirmed early attenuation of correlation coefficients in SAH mice, which persisted in predominantly posterior network connections at later time points. Seed-independent global and interhemispheric indices of connectivity revealed decreased correlations following SAH for at least 1 month. SAH led to MWM maze hidden platform and OFT deficits at 2-weeks, and Y-maze deficits for at least 3-months, without altering rotarod performance. In conclusion, experimental SAH leads to early and persistent alterations both in hemodynamically-derived measures of RSFC and in cognitive performance.

K-581. Early Prediction Of Time-to-awakening After Cardiac Arrest

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Introduction: In a multicenter cohort, we found withdrawal of life-sustaining therapies for perceived poor neurological prognosis occurs most commonly on the day of admission after cardiac arrest and contributes to preventable mortality. Early prediction of time-to-awakening could allow clinicians and families to understand the anticipated clinical course and outcome of post-anoxic coma.

Methods: We performed an observational study including comatose patients hospitalized after cardiac arrest at a single center from 2010 to 2019. Patients underwent targeted temperature management, admission brain CT, structured neurological examination and electroencephalography (EEG) started on admission. We performed an automated extraction of all electronic health record data. We quantified >5,000 features at 1Hz from the first 60min of EEG using Persyst, then summarized these to 48,298 time-invariant metrics. We considered standard demographic and arrest characteristics; initial neurological examination; initial multisystem organ failure (Sequential Organ Failure Assessment); Pittsburgh Cardiac Arrest Category (PCAC; a 4-level measure of illness severity based on presenting exam and cardiopulmonary failure); CT characteristics; and, medications administered during EEG. Our outcome was time to awakening. We randomly divided our sample into training (80%) and test (20%) sets, tuned a regularized Cox regression with a Lasso penalty in the training set using 5-fold cross-validation, then evaluated performance in the test set using C-index, log-rank P values by tertile and clinically relevant cutoffs.

Results: We included 1,031 subjects. Mean age was 58±17 years, 391 (38%) were female and 327 (32%) awakened after median 46 [IQR 29-84] hours. EEG was acquired 7 [IQR 5-9] hours from presentation. Our final model included 13 predictors including PCAC, initial motor examination, and 11 EEG measures of: delta- and beta-range spectral power, alpha- and beta-range rhythmicity, spike frequency and suppression ratio. Model performance in the test set was excellent (log-rank P<10e-5; C-index 0.74 (P<0.001 vs bootstrapped null)). Among those alive and comatose at 72h, the model (which incorporated only data available at presentation) had 94% sensitivity and 68% specificity to identify those who would still eventually awaken after a median 6.3 [IQR 4-11] days.

Conclusion: Parsimonious, interpretable models of presenting exam and quantitative EEG strongly predict time-to-awakening after cardiac arrest and identify recovery potential among those with persistent coma at 72h. This could provide clinicians and families early guidance about anticipated clinical course and prevent misguided nihilism and withdrawal.

K-600. Anti-seizure Drug Safety And Effectiveness In Aneurysmal Subarachnoid Hemorrhage

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Background: Higher burden of epilepitform abnormalities (EAs) is associated with worse outcomes in aneurysmal subarachnoid hemorrhage (aSAH) patients. There is limited data to guide management of EAs in these patients. Here we examine the safety and effectiveness of anti-seizure drugs (ASDs) in patients with aSAH.

Methods: We performed a retrospective analysis of 136 patients with high-grade aneurysmal aSAH who underwent continuous EEG monitoring. Presence and burden of EAs was recorded. We recorded the frequency of ASD prescription beyond standard prophylaxis. Clinical adverse effects and differences in survival between patients continued on ASDs vs. not were measured. Time to reduction in EA burden between patients continued on ASD vs. not was measured. At our center, prophylactic ASDs are discontinued after aneurysm treatment (within 2-3 days of admission). For this analysis, we only included patients with EAs on day 4 of admission.

Results: 66 patients (48.5%) were continued on ASD treatment. ASDs were more likely to be continued in patients with: higher first-24 hour EA burden (OR 1.96, p=0.001); higher APACHE II scores (OR 1.06; p=0.011); higher Hunt and Hess (OR 1.38, p=0.017) and higher Fisher scores (2.48;p=0.018). Although patients continued on ASDs were more likely to have clinical adverse effects of sedation (OR 1.53), rash (OR 1.31), hypotension (OR 1.71), and thrombocytopenia (OR 1.24), the only statistically significant adverse effect was hepatotoxicity (OR 3.30, p=0.004). The Kaplan-Meier survival did not show a difference in 90-day survival between patients continued on ASDs vs. those that were not (log rank test P=0.66). After stratification for maximum EA burden, and adjustment for age, APACHE II, and disease severity, although ASD continuation was associated

with a trend towards better survival, this was not statistically significant (hazard ratio 0.69, p=0.48). Among patients with EAs on day 4 of admission, we assessed differences in time to EA improvement over the next 72 hours of EEG monitoring. Mean time to improvement (decrease of EA burden < 1%) was 61 hours in those continued on ASDs vs. 69 hours in those who were not. After adjustment of day 4 EA burden, although patients continued on ASDs were more likely to have EEG improvement this was not statistically significant (HR 1.94, p=0.42).

Conclusion: ASD continuation was not associated with significant difference in survival, or significant difference in time to EA burden reduction. Prospective studies are needed to establish treatment risk benefit ratio.

Neurogenetics

131. Rapid-Onset Dystonia Parkinsonism: Evolution of Clinical Phenotype 26 Years Post Diagnosis

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Objective: To discuss the evolution of the clinical phenotype in a 49-year-old man with Rapid Onset Dystonia Parkinsonism (RDP) 26 years post diagnosis, and the heterogeneity associated with ATP1A3 mutations.

Background: RPD is a rare movement disorder characterized by the abrupt onset of parkinsonism and dystonia manifesting over hours to weeks in childhood or early adulthood. Our patient belongs to a family of 15 affected individuals spanning 3 generations who tested positive for a mutation in ATP1A3. This family was previously reported in Movement Disorders by Brashear et al.

Methods: We report on the evolution of the clinical phenotype in a 49-year-old man 26 years post diagnosis with RPD who was lost to follow up for 12 years and returned with worsening symptoms.

Results: At age 23 he reported cramps and tremor of the left hand, followed 2 months later by intermittent spasms of the left fifth toe lasting several weeks before resolving spontaneously. He described stiffness of the left leg while walking and cramping of the right hand. Examination demonstrated cogwheel rigidity at the left elbow, wrist and knee. Dystonic postures were noted in the left hand at rest that increased during walking. There was bradykinesia, but no tremor, postural instability, dysarthria, or dysphagia. A trial of levodopa/carbidopa demonstrated minimal improvement. 12 years later he underwent Deep Brain Stimulation with no benefit. Botulinum toxin injections, however, were helpful. He returned at the age of 49 with complaints of generalized stiffness and dysarthria. He had saccadic pursuit eye movements, facial dystonia, moderate-severe hypophonia with dystonic speech, generalized dystonia (most prominent in posterior neck and upper extremity muscles) and broad-based gait. There was symmetric rigidity, and bradykinesia of all extremities.

Conclusion: Dobyns et al. suggested a consistent and unique phenotype consisting of rapid onset dystonia and parkinsonism initially, with slow or no progression. We now know that a spectrum of clinical presentations are possible with the ATP1A3 mutations that include classic RDP, classic RDP with intermittent worsening, slowly progressive Dystonia Parkinsonism, alternating hemiplegia of childhood, alternating hemiplegia with evolution to dystonia parkinsonism, and combinations involving seizures and Cerebellar ataxia, Areflexia, Pes Cavus, Optic atrophy and Sensorineural hearing loss (CAPOS) syndrome. This may suggest that these diseases are not necessarily distinct clinical entities but perhaps different manifestations along a clinical spectrum of disease.

132. Familial Creutzfeldt Jakob Disease: Uncommon & Under-Recognized

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Introduction: Creutzfeldt Jakob disease (CJD) is a progressive, fatal, and irreversible degenerative brain disease resulting from misfolding of cell-surface brain protein known as cellular prion protein. Different types of CJD include sporadic CJD, acquired prion disease, and familial CJD. Familial CJD comprises 10% of CJD cases. It is under-recognized as it has a rapid onset, non-specific clinical presentation, and overlap in the differential diagnosis of Lewy body dementia and Alzheimer's disease. Here, we highlight a case of familial CJD.

Case: A 63-year-old man with a history of hypothyroidism and hypertension who presented with memory loss with dysarthria, gait disturbances, personality changes with psychosis, paranoid delusion, and auditory hallucination. On admission, he looked anxious, was startling to sound, had dysarthric speech, generalized tremulousness, and ataxic gait. Family history was strong for familial (autosomal dominant) CJD amongst 2 sisters, father, and paternal grandmother. One of his sisters had genetic testing done in 2004 showing PRNP (Prion Protein) mutation when another sister was diagnosed. His MRI brain showed T2 hyperintensity and diffuse restriction on DWI throughout the cerebral cortex except for the occipital lobes, the basal ganglia bilaterally, and the medial thalami, consistent with the diagnosis of CJD. His EEG was normal. Due to his strong family history, further workup such as a lumbar puncture was deferred. For agitation and paranoia, he was started on antipsychotics & mood stabilizers which showed good response. Since he had progressive degenerative disease with guarded prognosis, he was not a candidate for rehabilitation. He was discharged to a skilled nursing facility where he passed away the following month. He did not have any children; his siblings were offered genetic counseling.

Conclusion: We aim to increase the awareness of familial CJD. This will help to deal with families affected by genetic prion disease by offering asymptomatic genetic testing. It will aid in future financial planning, family planning, or participation in research studies.

133. Age-at-Onset and Time-to-Event of Core Features in CLN3 (Batten) Disease

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Objective: To determine the age-at-onset of core clinical features of CLN3 disease and how they align with parent priorities.

Background: CLN3 disease (Juvenile Batten Disease) is characterized by vision loss, epilepsy, dementia, and a movement disorder. Most individuals also have disordered behavior, sleep, and feeding. Knowing the age-at-onset and meaningfulness of these core features can inform the design of future clinical trials.

Design/Methods: We used the Unified Batten Disease Rating Scale (UBDRS), to collect natural history data on CLN3 disease over 17 years, including estimated age-at-onset of core features. Separately, we asked 57 parents about treatment priorities.

Results: We obtained data from 102 individuals and found a characteristic sequence of symptom onset with small but significant sex differences (t-test; $p<0.05$*). The average ($\pm$SD) symptom age-at-onset (in years) was: vision (Male: 5.6 $\pm$ 1.5 Female: 6.6 $\pm$ 1.6)*, behavior (M: 7.4 $\pm$ 3.8 F: 8.4 $\pm$ 4.0)*, cognition (M: 8.0 $\pm$ 3.5 F: 8.1 $\pm$ 3.0), seizures (M: 9.9 $\pm$ 2.7 F: 10.0 $\pm$ 2.0), sleep (M: 8.9 $\pm$ 5.4 F: 11.1 $\pm$ 5.6)*, motor (M: 12.1 $\pm$ 4.1 F: 10.9 $\pm$ 3.8), and feeding (M: 19.8 $\pm$ 2.5 F: 16.4 $\pm$ 2.9)*. For the total sample the average time from onset of one feature to the next was 2 years. Major parent-reported symptom priorities included vision (21%), seizures (24%), dementia (16%), motor/mobility (22%), and mood/behavior (10%).

Conclusion: CLN3 disease progresses in a characteristic manner at a predictable rate based on time and sequence of core symptom onset, with slight sex differences for some symptoms. The core symptoms aligned well with the parent priorities, indicating that these symptoms are meaningful to families. Our results support the possible use of a time-to-event analysis in experimental therapeutic research. Used in combination with measures of symptom severity, these data contribute to a comprehensive picture of CLN3 disease natural history.

134. Cross-Sectional and Longitudinal Natural History of CLN3 Disease Progression

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Objective: To quantify the relationship between symptom severity and age in CLN3 disease using both cross-sectional and longitudinal analyses.

Background: CLN3 disease (Juvenile Batten Disease) is a neurodegenerative disease beginning in early childhood and progressing until death in the third decade of life.

Design/Methods: Participants were evaluated using the Unified Batten Disease Rating Scale (UBDRS), a disease-specific rating scale with four subscales: physical, seizure, behavioral, and functional capability. The most recent evaluation for each participant, including those with only a single time point, was used to perform cross-sectional analyses. For individuals with multiple time points, longitudinal analyses were performed accounting for the effect of multiple within-subject evaluations.

Results: We analyzed data from 126 unique individuals with a total of 380 evaluations. 47 individuals were evaluated at a single time point; 79 individuals had serial evaluations with up to 15 assessments per individual. In both cross-sectional and longitudinal analyses, the physical, seizure**,** and functional capability scores correlated with age. The behavior score did not correlate with age. The annual rate of physical progression was 3.02 $\pm$ 0.24 (slope $\pm$ SE) points (cross-sectional) and 3.11 $\pm$ 0.28 points (longitudinal). The annual rate of seizure progression was 0.53 $\pm$ 0.10 points (cross-sectional) and 0.59 $\pm$ 0.08 points (longitudinal). The annual rate of functional capability change was 0.53 $\pm$ 0.06 points (cross-sectional) and 0.60 $\pm$ 0.04 points (longitudinal).

Conclusion: Our data provide a global assessment of CLN3 disease severity and show a nearly linear rate of relentless progression after onset. Cross-sectional and longitudinal analyses yielded similar results, supporting the combination of cross-sectional with longitudinal approaches to increase sample size in this rare disease. They also suggest the potential for combining such data as a baseline for future clinical trials in CLN3 disease. Used in combination with symptom age-at-onset, these data provide a comprehensive picture of CLN3 disease natural history.

K-585. Genome-edited Human Hematopoietic Stem Cells Correct Lysosomal Storage Disorders

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Lysosomal storage diseases (LSDs) are a group of more than 50 genetic disorders involving lysosomal dysfunction, most of which lack effective treatments. The need to intervene and improve outcomes has driven the establishment of newborn screening programs for some LSDs, like MSPI, though the real benefit of these programs is bound by the limited efficacy of the therapies. Current interventions available for a minority of LSDs are enzyme replacement therapy (ERT) and allogeneic hematopoietic stem cell transplantation. Generally, these approaches at best slow disease progression. **A potentially safer, more effective approach is to engineer the patient's own hematopoietic system to secrete high levels of the relevant lysosomal enzyme.** We have established an efficient genome-editing strategy where lysosomal enzymes are specifically targeted to the human *CCR5* safe-harbor locus. Such an approach constitutes an adaptable "one size

fits many" platform that is independent of specific lysosomal enzymes or patient mutations. We used this strategy to engineer human hematopoietic stem and progenitor cells (HSPCs) to express iduronidase (IDUA) and glucocerebrosidase (GCase), the deficient enzymes in MPSI and Gaucher disease, the two most common LSDs. The cells were engineered to produce supra-physiological enzyme levels for IDUA using a constitutive promoter or with lineage-specific expression in the monocyte/macrophage for GCase. We find that the neither the genome editing approach, nor the enzyme expression affect the cells' potential to differentiate into multiple hematopoietic lineages. Specifically, HSPCs expressing GCase generated functional human macrophages; the affected cells in this disease. Long-term and serial engraftment studies in immunocompromised mice demonstrate modification of cells with long-term repopulating capacity, albeit at lower efficiency than progenitors. The efficacy of the modified cells was demonstrated using a novel MPSI mouse model for human cell engraftment. Transplantation of cells overexpressing IDUA in these mice showed improvements in biochemical, bone, and neurobehavioral pathology. Genotoxicity was examined by characterization of the off-target repertoire of our *CCR5* guide using COSMID and deep sequencing. The modified cells showed normal p53 activity and sequencing of 198 genes frequently mutated in tumors did not identify any recurrent mutations. Our studies provide proof-of-concept evidence of the safety and efficacy of using genome-edited human HSPCs modified to express a lysosomal enzyme to correct the biochemical, structural, and behavioral phenotypes in MPSI. The potential for this approach to become a platform for treating other LSDs is supported by our studies in Gaucher disease.

K-593. **Infantile Spasms In CDKL5 Deficiency Disorder Respond Poorly To First Line Treatments**

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Background: Epilepsy in CDKL5 Deficiency Disorder (CDD) is highly refractory (Olson et al. Pediatric Neurology 2019). We aimed to evaluate response of IS to first-line treatments and ketogenic diet in patients with CDD compared to controls.

Methods: We evaluated patients with IS onset 2 months to 2 years (2012 to 2019) from 2 cohorts: patients with CDD seen in the CDKL5 Centers of Excellence and patients from the National Infantile *Spasms* Consortium (NISC) database. We excluded controls with Tuberous Sclerosis Complex, Trisomy 21 or unknown etiology with normal development. We compared clinical response (spasm freedom) at 14 days and 3 months for ACTH, prednisolone, vigabatrin, and ketogenic diet.

Results: Forty-five patients with CDD had IS onset at median 5.0 months [IQR 3.0, 7.0] and 375 patients from the NISC database had IS onset at median 6.5 months [IQR 4.5, 8.7]. Treatment response in CDD was worse than in controls. In patients with CDD, ACTH was used in 38%, prednisolone in 40%, and vigabatrin in 67%. The 14-day response was 23% (4/17) for ACTH, 12% (2/17) for prednisolone, 27% (7/26) for vigabatrin and the 3 month response was 0% (0/8) for ACTH, 0% (0/ 6) for prednisolone and 11% (2/19) for vigabatrin. In control patients, ACTH was used in 60%, prednisolone in 40% and vigabatrin in 53%. The 14-day clinical response was 63% (138/219) for ACTH, 53% (51/ 97) for prednisolone, and 42% (77/184) for vigabatrin and the 3 month response was 59% (128/217) for ACTH, 54% (45/84) for prednisolone, 42% (78/184) for vigabatrin. Ketogenic diet was used for refractory IS in 53% of patients with CDD and 14% of controls. There was equivalent 1 month response, 20% (4/20) patients with CDD and 19% (23/27) controls but lower 3 month response in CDD, 17% (2/12) patients with CDD compared to 38% (15/40) controls.

Conclusions: Response of infantile spasms to ACTH, prednisolone and vigabatrin is worse in CDD compared to IS in the available NISC data and published literature. Vigabatrin was most frequently used in the CDD cohort and had the best response (27% at 14 days). Ketogenic diet had similar efficacy in CDD at 1 month but lower efficacy at 3 months suggesting possible transient response. We suggest considering initial treatment with ketogenic diet in combination with first-line therapy or after one failed treatment for IS in CDD.

K-594. **Genetic Risk-Associations Causally Implicate Viral Response Pathways In Dementia With Tau Pathology**

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Recent genetic discoveries point to causal roles for glial immune-associated genes in specific neurodegenerative diseases. Understanding how these genes translate into signaling pathways and affect cellular function at the whole-genome level promises direct insight into disease pathobiology. We reasoned that gene co-expression networks enriched for genetic risk variants could specify causal disease biology. We combined pooled cell and bulk brain transcriptomic analysis to define stage- and cell-type associated gene co-expression networks (modules) in mouse models of tau-induced neurodegeneration. We found that the microglia transitions from early to late disease stages bear resemblance to viral infections that trigger chronic inflammation. We studied the relationship between these refined disease modules and genetic variants associated with Alzheimer's disease (AD), Progressive Supranuclear Palsy (PSP), and Frontotemporal dementia (FTD). We found that that modules related to viral response and defense mechanisms specifically enrich for PSP, FTD and AD genetic risk variants, further linking viral defense mechanisms to disease causality. We are now extending these analyses to directly interrogate human tissue from AD, FTD and PSP to assess similarities and differences in viral-related neuroinflammatory pathways across these disorders.

114. Schwann Cells with Fig4 Deficiency are Predisposed to Demyelination

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Objectives: Segmental demyelination consistently occurs in patients with Charcot-Marie-Tooth disease type-4J (CMT4J) caused by recessive mutations in *FIG4* gene. Our previous study has demonstrated an increased intracellular Ca^{2+} in FIG4 deficient Schwann cells due to lysosomal Ca^{2+} channel dysfunction. In this study, we tested a hypothesis that whether FIG4 deficient Schwann cells are sensitized to demyelinate upon the challenge of extra Ca^{2+}.

Methods: Surgically exposed sciatic nerve in 3-month-old *Fig4*$^{f/f}$ and Schwann cell conditional knockout (*scFig4*$^{-/-}$) mice was wrapped by gauze soaked with 10μM Ca^{2+} Ionophore A23187, while the contralateral sciatic nerve was treated with vehicle for 3 hours. The mice were allowed to recover for 10 days, followed by nerve conduction studies and teased nerve fiber analysis for counting segmental demyelination.

Results: A23187 significantly decreased conduction velocity (CV) in *scFig4*$^{-/-}$ nerves, compared with that in vehicle-treated *scFig4*$^{-/-}$ nerves (A23187 8.8±0.8 m/s vs. vehicle 13.4±3.0 m/s; $p<0.01$, n=5 for each group). A23187 did not affect CV in *Fig4*$^{f/f}$ nerves (A23187 30.0±3.2 m/s vs. vehicle 28.8±4.0 m/s; $p>0.05$; n=5). Segmental demyelination was observed in 9.0±1.1% of nerve fibers from *scFig4*$^{-/-}$ nerves treated with A23187, 2.2±0.2% in *scFig4*$^{-/-}$ nerves treated with vehicle, 2.3±0.4% in *Fig4*$^{f/f}$ nerves treated with A23187, and or 2.0±0.6% in *Fig4*$^{f/f}$ nerves treated with vehicle ($p<0.01$, 100-200 fibers counted/mouse, n=5 mice for each group). Segmental demyelination was associated with an increase of Schwann cell dedifferentiation factor c-Jun level.

Conclusions: FIG4-deficiency impairs the capacity of Schwann cells to "buffer" extra Ca^{2+}, thereby sensitizing the cells to demyelination. In a live animal, the extra Ca^{2+} in Schwann cells could be induced by axon excitation or cytokines released from macrophages.

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115. Loss of CHCHD2 and CHCHD10 Activates Oma1 Peptidase to Disrupt Mitochondrial Cristae Phenocopying Patient Mutations

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Dominant mutations in the mitochondrial paralogs CHCHD2 (C2) and CHCHD10 (C10) were recently identified as causing Parkinson's disease and ALS/FTD/myopathy, respectively, and are associated with disruption of mitochondrial cristae in patient cells and tissues. Recently C10 knock-in (KI) mice were observed to develop a fatal cardiomyopathy associated with mitochondrial cristae abnormalities. The mechanism by which dominant C10 mutations cause mitochondrial cristae defects and their relationship to C2/C10 normal function, however, have been unclear. Here we report that C2/C10 double knockout (DKO) mice phenocopy C10 KI mice and C10 patients, developing both mitochondrial cristae defects and cardiomyopathy. We further identified activation of the stress-induced peptidase OMA1, leading to the excessive cleavage of L-OPA1, as the mechanism driving abnormalities in mitochondrial cristae. L-OPA1 processing defects could be restored by exogenous expression of either C2 or C10, demonstrating functional redundancy between the paralogs. Unexpectedly, overexpression of C2 or C10 also activated OMA1, mimicking C2/C10 loss of function. Thus, C2 and C10 levels must be maintained within a narrow range for balanced OPA1 processing. Activated OMA1 was likewise observed in tissues from C10 KI mice. We propose a model by which dominant mutations in C10 may change the effective concentration of C2/C10 thereby disrupting mitochondrial cristae and phenocopying C2/C10 loss of function. Taken together our findings establish imbalanced OPA1 as the mechanism underlying cristae defects due to C2/C10 loss or mutation and tie mutant pathogenesis to C2/C10 physiologic function.

116. An Undiagnosed White Matter Disorders Neurogenetics Clinic

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While most adult-onset white matter disorders are due to acquired etiologies (inflammatory demyelinating disorders like multiple sclerosis, systemic autoimmune disorders with a central nervous system component, vascular disorders, toxic leukoencephalopathies and headache), there are a small proportion of adults that do not meet diagnostic criteria for these disorders. Adults with bilateral white matter abnormalities on brain MRI that are atypical for more common disorders, with or without a family history of leukodystrophy or leukoencephalopathy, were referred to an Undiagnosed White Matter Disorders Neurogenetics Clinic at the University of Pennsylvania. Patients were evaluated in collaboration with a genetic counselor. There were 35 patients evaluated in 14 clinics. Twenty-six patients underwent genetic testing (including whole exome sequencing (WES), targeted gene panels, single gene testing, or mitochondrial sequencing), along with a serum evaluation to rule out metabolic and rare acquired inflammatory demyelinating disorders (like neuromyelitis optica or MOG-antibody associated disorder). Six patients did not undergo genetic testing (either because they did not have a white matter disorder (n=2), they already had a genetic diagnosis (n=2), or they were recommended to get testing but have not yet done so (n=2)), and three patients have pending results. A genetic diagnosis was made in 30.8% (8/26), including adult polyglucosan body disease (n=1), X-

linked adrenoleukodystrophy (n=4), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (n=1), spastic paraplegia 11 (n=1), and CSF1R-related leukoencephalopathy (n=1). Variants of uncertain significance (VUS) were identified in 26.9% (7/26). Genetic testing was unrevealing in 42.3% (11/26). A diagnosis of atypical multiple sclerosis or other acquired disorder could not be definitively excluded in 2 patients with VUS, and 4 patients with negative WES. Neuromyelitis optica was newly diagnosed in one patient. Of the two patients with prior diagnoses, one was an asymptomatic adult male whose daughter was identified as a carrier of X-linked adrenoleukodystrophy on the newborn screen, and the other an adult female with L2-hydroxyoglutaric aciduria diagnosed in childhood. Adults with white matter abnormalities of presumed genetic etiology remain unsolved in approximately two thirds of all affected patients referred for a diagnosis. To reduce the proportion of unresolved cases, we intend to employ more comprehensive clinical genetic testing (such as whole genome sequencing), as well as develop a pipeline to study the pathogenicity of variants of uncertain significance.

117. *FTH1De Novo* Dominant Variants Alter Iron Metabolism and Cause a Pediatric Onset Neuroferritinopathy

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Ferritin, the iron storage protein crucial for regulating cellular iron metabolism, is composed of heteropolymers of light chain and heavy chain subunits. Heterozygous mutations in the ferritin light chain, encoded by *FTL*, lead to neuroferritinopathy, a disorder with abnormal brain iron deposition and clinical manifestations overlapping with the genetically-heterogeneous NBIA (neurodegeneration with brain iron accumulation) syndromes. Here we report two unrelated patients with *de novo* heterozygous variants in *FTH1*, encoding the ferritin heavy chain, with a pediatric onset neuroferritinopathy. Individuals presented in childhood with neurodevelopmental delays, with subsequent onset of prominent ataxia and progressive neurologic regression. Neuroimaging demonstrated progressive cerebellar atrophy and iron accumulation in the basal ganglia. By neuropathology iron accumulates and demonstrates cavitary lesions and discoloration of several regions of the brain like the putamen, globus pallidus, and substantia nigra. Using *FTH1*- patient-derived fibroblasts we show increased expression of both chains of ferritin, and ferritin aggregates visible by immunocytochemistry. We also found that *FTH1*-patient fibroblasts exhibit higher levels of iron accumulation and lipid peroxidation upon exposure to iron. Structural modeling of the *FTH1* variants identifies a truncation of the E-helix, likely leading to altered pore size in the heteropolymer and therefore impaired Fe storage capacity. Furthermore, similar to FTL-associated neuroferritinopathy, we found evidence of oxidative protein damage and alterations in GPX4 activity, suggesting altered iron homeostasis may ultimately alter pathways associated with ferroptosis. This is the first report of a de novo dominant neurodevelopmental phenotype associated with *FTH1* variants.

118. Early Experience with Hematopoietic Stem Cell Transplant for Adult Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia

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Background: Adult onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a fatal autosomal dominant adult-onset progressive leukodystrophy characterized by dementia and parkinsonism. Mutations in the *CSF1R* gene, which encodes macrophage colony-stimulating factor receptor expressed by microglia, are associated with ALSP. While preliminary data have indicated that progression of ALSP may be delayed with hematopoietic stem cell transplantation (HCT), additional studies are critical to advance HCT practice. Here we report initial experience with two adults with *CSF1R* mutations who have undergone HCT for ALSP.

Methods: Patients were enrolled at the University of Minnesota under clinical trial MT2013-31 (Allo HCT for Metabolic Disorders and Severe Osteopetrosis).

Results: Patient 1 has a Q642X nonsense mutation in *CSF1R* and initially presented with memory and behavioral problems at age 44. Though tested portions of mental status exam were unremarkable, perseveration and disinhibition were noted. The remainder of the exam was normal. MRI showed confluent frontal-predominant white matter T2 hyperintensities and patchy restricted diffusion with faint enhancement. The patient underwent myeloablative HCT using bone marrow from a matched unrelated donor. Post-transplant course was complicated by mild graft-versus-host disease (GVHD) of the upper GI tract and and delayed neutrophil recovery. Post-transplant, the patient had cognitive changes reported by family after administration of G-CSF to treat neutropenia, with abulia and incomplete recovery. Neurological exam 12 months post-HCT was significant for impaired mental status, with orientation only to self. The remainder of the patient's examination and imaging were stable at 12 months.Patient 2 has a W893R mutation in *CSF1R* and initially presented to clinic with difficulty walking at age 46 years. Neurological examination showed normal mental status testing, brisk reflexes and parkinsonism. MRI demonstrated confluent T2 hyperintensities in the periventricular white matter without restricted diffusion or enhancement. The patient underwent

myeloablative HCT with a matched sibling donor, with an uncomplicated post-transplant course. At 6 month follow-up, the patient's neurological exam and MRI remained stable.

Conclusion: HCT represents a promising disease-modifying treatment for ALSP. These cases advance our understanding of HCT application, demonstrating potential benefits and risks of transplantation. Longer follow-up is necessary to further establish the safety and efficacy. The reaction of Patient 1 following administration of G-CSF is interesting. These findings will require further investigation to contextualize, particularly focused on heterogeneity in clinical symptoms, neuroimaging, and genetic mutations.

119. ADNC-RS, a Clinical-Genetic Risk Score, Predicts Alzheimer's Pathology in Autopsy-Confirmed Parkinson's Disease and Dementia with Lewy Bodies

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Growing evidence suggests overlap between Alzheimer's disease (AD) and Parkinson's disease (PD) pathophysiology in a subset of patients. Indeed, 50-80% of autopsy cases with a primary clinicopathological diagnosis of Lewy body disease (LBD) - most commonly manifesting during life as PD - have concomitant amyloid-beta and tau pathology, the defining pathologies of AD. Here we evaluated common genetic variants in genome-wide association with AD as predictors of concomitant AD pathology in the brains of people with a primary clinicopathological diagnosis of PD or Dementia with Lewy Bodies (DLB), diseases both characterized by neuronal Lewy bodies. 208 consecutive autopsy-confirmed cases of PD or DLB were assessed for AD neuropathological change (ADNC), and these same cases were genotyped at 20 single nucleotide polymorphisms (SNPs) found by genome-wide association study to associate with risk for AD. In a training set of the first 127 individuals, we developed a logistic regression model predicting the presence of ADNC, using backward stepwise regression for model selection and 10-fold cross-validation to estimate performance. We then assessed model performance in a separate test set of the next 81 individuals. The best-fit model generated a risk score for ADNC (ADNC-RS) based on age at disease onset and genotype at three SNPs (*APOE*, *BIN1*, and *SORL1* loci). In the training set, the area under the receiver operating curve (AUC) for this model was 0.751. In the test set, the AUC was 0.781. Individuals with ADNC-RS in the top quintile had four-fold likelihood of having AD pathology at autopsy compared with those in each of the lowest two quintiles. In patients with autopsy-confirmed PD or DLB a simple model incorporating three AD-risk SNPs and age at disease onset substantially enriches for concomitant AD pathology at autopsy, with implications for identifying LBD patients in which targeting amyloid-beta or tau is a therapeutic strategy.

120. The Chromatin Remodeling Enzyme Chd4 Regulates Genome Architecture in the Mouse Brain

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The development and function of the brain require tight control of gene expression. Genome architecture is thought to play a critical regulatory role in gene expression, but the mechanisms governing genome architecture in the brain *in vivo* remain poorly understood. Here, we report that conditional knockout of the chromatin remodeling enzyme Chd4 in granule neurons of the mouse cerebellum increases accessibility of gene regulatory sites genome-wide *in vivo*. Conditional knockout of Chd4 promotes recruitment of the architectural protein Cohesin preferentially to gene enhancers in granule neurons *in vivo*. Importantly, *in vivo* profiling of genome architecture reveals that conditional knockout of Chd4 strengthens interactions among developmentally repressed contact domains as well as genomic loops in a manner that tightly correlates with increased accessibility, enhancer activity, and Cohesin occupancy at these sites. Collectively, our findings define a role for chromatin remodeling in the control of genome architecture organization in the mammalian brain.

121. Prevalence of *RFC1*-Mediated Spinocerebellar Ataxia in a North American Ataxia Cohort

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Objective: We evaluated the prevalence of pathogenic repeat expansions in *RFC1 and DAB1* in an undiagnosed ataxia cohort from North America.

Methods: A cohort of 596 predominantly adult-onset patients with undiagnosed familial or sporadic cerebellar ataxia were evaluated at a tertiary referral ataxia center and excluded for common genetic causes of cerebellar ataxia. Patients were then screened for the presence of pathogenic repeat expansions in *RFC1* (AAGGG) and *DAB1* (ATTTC) using fluorescent repeat primed polymerase chain reaction (RP-PCR). Two additional undiagnosed ataxia cohorts from different centers, totaling 302 and 13 patients respectively, were subsequently screened for *RFC1* resulting in a combined 911 subjects tested.

Results: In the initial cohort, 41 samples were identified with one expanded allele in the *RFC1* gene (6.9%), and 9 had two expanded alleles (1.5%). For the additional

cohorts, we found 20 heterozygous samples (6.6%) and 17 biallelic samples (5.6%) in the larger cohort, and 1 heterozygous sample (7.7%) and 3 biallelic samples (23%) in the second. In total, 29 patients were identified with biallelic repeat expansions in *RFC1* (3.2%). Of these 29 patients, 8 (28%) had a clinical diagnosis of CANVAS (cerebellar ataxia, neuropathy, and vestibular areflexia syndrome), 14 had cerebellar ataxia with neuropathy (48%), 4 had pure cerebellar ataxia (14%), and 3 had spinocerebellar ataxia (10%). No patients were identified with expansions in the *DAB1* gene (Spinocerebellar Ataxia type 37).

Conclusion: In a large undiagnosed ataxia cohort from North America, biallelic pathogenic repeat expansion in *RFC1* was observed in 3.2%. Testing should be strongly considered in ataxia patients, especially those with CANVAS or neuropathy.

122. A Diagnostic Ceiling for Exome Sequencing in Cerebellar Ataxia and Related Neurological Disorders

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Genetic ataxias are associated with mutations in hundreds of genes with high phenotypic overlap complicating clinical diagnosis. Whole exome sequencing (WES) has increased the overall diagnostic rate considerably. However, the upper limit of this method remains ill-defined, hindering efforts to address the remaining diagnostic gap. To further assess the role of rare coding variation in ataxic disorders, we reanalyzed our previously published exome cohort of 76 predominantly adult and sporadic onset patients, expanded the total number of cases to 260, and introduced analyses for copy number variation and repeat expansion in a representative subset. For new cases (n=184), our resulting clinically relevant detection rate remained stable at 47% with 24% classified as pathogenic. Reanalysis of the previously sequenced 76 patients modestly improved the pathogenic rate by 7%. For the combined cohort (n=260), the total observed clinical detection rate was 52% with 25% classified as pathogenic. Published studies of similar neurological phenotypes report comparable rates. This consistency across multiple cohorts suggests that, despite continued technical and analytical advancements, an ~50% diagnostic rate marks a relative ceiling for current WES-based methods and more comprehensive genome-wide assessment is needed to identify the missing causative genetic etiologies for cerebellar ataxia and related neurodegenerative diseases.

123. Peripheral Nerve Toxicity of Sulfatide in Metachromatic Leukodystrophy

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Objective: Metachromatic leukodystrophy (MLD) is a lysosomal storage disease caused by arylsulfatase A (ASA) deficiency, which results in sulfatide accumulation and demyelination in the central and peripheral nervous systems. We previously identified a cross-sectional relationship between peripheral nerve sulfatide levels and demyelination (Dali *et al.*, *ACTN*, 2015). Here, we aimed to explore further the relationship between sulfatide levels and pathological changes in the nervous system in children with MLD using longitudinal data from the clinical trials of intravenous recombinant human (rh) ASA.

Methods: Thirteen children with late-infantile MLD (age, 2.1-4.9 years) received intravenous rhASA every 2 weeks for up to 78 weeks (NCT00418561; NCT00633139; NCT00681811). Sulfatide levels were measured in the cerebrospinal fluid (CSF) at baseline and 10, 26, 52 and 78 weeks, and in the sural nerves at baseline and 26 weeks. Clinical and paraclinical measures included: motor performance, assessed by Gross Motor Function Measure-88 (GMFM-88) total score; light and electron microscopy of sural nerve biopsies at baseline and 26 weeks; *N*-acetylaspartate (NAA) levels in the brain; and motor and sensory nerve conduction studies of the median, fibular and sural nerves.

Results: At baseline, CSF and sural nerve sulfatide levels were markedly higher than those observed in children without MLD; sural nerve biopsies and conduction studies indicated severe demyelination in 11 of the 13 children. Overall, nerve conduction and morphology remained relatively stable over the course of the studies, whereas GMFM-88 total scores and brain NAA levels decreased over time. CSF sulfatide levels showed a strong negative correlation ($p<0.005$) with the number of myelinated sural nerve fibers, and with conduction velocities and amplitudes in motor and sensory nerves. There was no correlation between CSF sulfatide and axon diameters, but a strong positive correlation between CSF sulfatide and g-ratios ($p<0.005$). Similarly, sural nerve sulfatide levels negatively correlated with nerve conduction ($p<0.05$) and the number of large myelinated nerve fibers ($p<0.01$). In contrast, there was no correlation between CSF or sural nerve sulfatide levels and GMFM-88 total scores or NAA levels.

Conclusions: The strong relationship between sulfatide levels and peripheral nerve pathophysiology over time supports a primary toxic effect of sulfatide on peripheral myelin,

ultimately leading to axon degeneration. These findings emphasize the importance of reducing peripheral sulfatide accumulation to preserve peripheral nerve function in patients with MLD. Shire (a Takeda company) sponsored this study and funded writing support.

124. Biodistribution of Spherical Nucleic Acids in the Nonhuman Primate Central Nervous System

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Background and Objective: Spherical nucleic acids (SNA™) are nanostructures comprised of densely packed oligonucleotides, radially arranged around a lipid core. Prior work indicates that: i) SNA exhibit improved cellular uptake and target affinity relative to their linear counterparts, ii) SNA-formulated nusinersen extends survival of spinal muscular atrophy mice following intracerebroventricular delivery, and iii) intrathecally-delivered SNA distribute throughout the rat central nervous system (CNS). Here, our aim was to determine the tolerability and biodistribution of SNA in the nonhuman primate (NHP) CNS.

Methods: We intrathecally administered a single dose of SNA bearing ^{124}I-labeled 2′-O-methoxyethyl, fully-phosphorothioate antisense oligonucleotides to adult male cynomolgus monkeys and monitored biodistribution in six peripheral tissues, 3 circulating biofluids and 46 CNS regions by positron emission and computed tomography. Animals were imaged immediately following injection and intermittently up to 14 days post-injection. Upon completion of the study, gross histopathology was assessed.

Results and Discussion: SNA distributed widely throughout the NHP CNS and persisted in key regions affected in genetically-defined ataxia disorders, including the cerebellum, midbrain, substantia nigra, diencephalon and spinal cord. Standardized uptake values in these and other regions persisted above ½-maximal for 14 days. In contrast to published data on typical "linear" oligonucleotides (i.e. unformulated oligonucleotides not in the SNA format), SNA were not preferentially excreted through kidneys. Histopathology revealed minimal infiltration of mononuclear cells at the injection site in some NHPs that was not associated with clinical signs. No adverse events were reported in any animals.

Conclusion: Intrathecally-delivered SNA readily permeate the entire NHP CNS and persist for at least two weeks, reaching vital regions affected in ataxia-related disorders. Further, SNA were safe and well-tolerated in NHP. These data support the development of SNA as therapeutics for genetically-defined ataxias and other neurodegenerative disorders.

125. Rapid Identification of Polymicrobial Pathogens Using Nanopore 16s Amplicon Sequencing in the Patients with Brain Abscess

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Objective: Brain abscess is medically challenging infectious disease, and early detection of pathogen is crucial to find proper antibiotics specific to the pathogen in addition to treatment with surgical aspiration and removal. Metagenomic sequencing is useful for identifying certain pathogen that are difficult to cultivate by conventional culture studies. Especially, 16s ribosomal DNA (16s rDNA) amplicon sequencing is suited for bacterial identification. In this study, we applied nanopore sequencing for the analysis of 16S rDNA sequence from the specimen of brain abscess and investigated its efficacy and diagnostic value.

Methods: Twenty-five samples were collected from 22 patients diagnosed with brain abscess, and among the samples, there were follow-up samples of three cases of resurgery. Genomic DNA was extracted from pus or aspiration specimen of the abscess pocket obtained in the neurosurgery operation room. After running PCR using universal bacterial 16S primers, 27F and 1492R, the 16S rRNA genes were amplified, and the sequencing libraries were generated from the PCR product using rapid barcoding kit (SQK-RBK004). The generated reads were analyzed using Epi2Me 16S workflow. Conventional culture study was performed from the same specimen of the abscess pocket, and the result of each diagnostic method was reviewed and analyzed.

Results: Turnaround time for all cases of 16S sequencing took less than 24 hours, while the median time for the conventional culture study was 4 days [2-10]. Among the pathogens identified, proportion of anaerobic bacteria was higher in 16S sequencing (67%) than that in the culture study (32%). Polymicrobial infections were revealed in 10 cases (40%) by 16S sequencing (40%), however culture study have cultivated multiple bacteria in only 2 cases (8%). Moreover, no bacteria was isolated in 6 cases (24%) by culture study. 16S sequencing was useful for identifying rare pathogen such as *Campylobacter* or *Fusobacterium* which does not easily grow in the conventional culture system.

Conclusions: In conclusion, 16S sequencing was capable of rapid identification of pathogen in brain abscess patients. It also provided much information about presence of polymicrobial infection and aerobic or anaerobic features of the pathogen. Further study with larger number of cases would be warranted to explore diagnostic potential of the nanopore 16S sequencing in various conditions of infection.

126. Amelioration of Brain Histone Methylopathies by Balancing a Writer-Eraser Duo Kmt2a-Kdm5c

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Histone H3 lysine 4 methylation (H3K4me) is extensively regulated by seven writer and six eraser enzymes in mammals. Nine H3K4me enzymes are associated with neurodevelopmental disorders to date, indicating their important roles in the brain. Opposing activities of writer-eraser enzymes highlight activity modulation as a therapeutic strategy. However, interplay among H3K4me enzymes in the brain remains largely unknown. Here, we show functional

interactions of a writer-eraser duo, KMT2A and KDM5C, which are responsible for Wiedemann-Steiner Syndrome (WDSTS), and mental retardation X-linked syndromic Claes-Jensen type (MRXSCJ), respectively. Despite opposite enzymatic activities, the WDSTS and MRXSCJ mouse models, deficient for either Kmt2a or Kdm5c, shared reduced dendritic spines and increased aggression. Double mutation of Kmt2a and Kdm5c clearly reversed dendritic morphology deficits and key behavioral traits including aggression, and partially corrected altered transcriptomes and H3K4me landscapes. Thus, our study uncovers common yet mutually suppressive aspects of the WDSTS and MRXSCJ models and provides a proof of principle for balancing a single writer-eraser pair to ameliorate their associated disorders.

127. Novel Putative TUBB4 Mutation in a Case of Leukodystrophy with Demyelinating Peripheral Neuropathy

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Objective: To describe a novel putative TUBB4A mutation in a case of leukodystrophy with demyelinating peripheral neuropathy.

Background: TUBB4A-related disorders have a wide clinical spectrum ranging from hypomyelination with atrophy of the basal ganglia and cerebellum to torsion dystonia. Demyelinating neuropathies are seen in some, but not all leukodystrophies. PNS involvement is seen in Krabbe's and Metachromatic leukodystrophy, but to our knowledge, demyelinating polyneuropathies have not been reported as part of TUBB4A-associated disorders.

Case Description: We present a 27-year-old male with learning disability, gait, and balance difficulties. The symptoms started at 17 years of age with progressive walking difficulties. Family history was negative for any neurological disorders. On physical examination he had increased muscle tone in all extremities with cog wheeling and fine intention tremors in the upper extremities. Sensory examination demonstrated decreased vibratory sense in the lower extremities. Diffuse hyper-reflexia and non-extinguishing ankle clonus were noted. Clinical signs for cerebellar dysfunction including dysmetria, dysdiadochokinesia, and truncal ataxia were present. His gait was spastic and ataxic. The initial work was negative for vitamin deficiencies and infections, with normal inflammatory markers. Long chain fatty acids and a hereditary spastic paraparesis panel were negative. Brain MRI demonstrated moderate to severe central and moderate peripheral brain atrophy. Bilateral symmetrical T2/FLAIR hyperintensities consistent with deep white matter disease in the bilateral parietal-occipital junctions, parietal lobes, and occipital lobes was seen. EMG/NCS findings were consistent with a sensorimotor demyelinating polyneuropathy. Whole exome sequencing revealed a heterogenous variant of uncertain significance in the TUBB4A gene (chr 19:6496224C>T; NM_001289123.1:c.439G>A; NP_001276052.1:p.Gly147Arg). This variant is not present in the gnomAD database and four out of six functional prediction algorithms predict this variant to be damaging.

Conclusion: Our patient presented with gait and balance difficulties due to both central and peripheral nervous system deficits, with white matter abnormalities in brain MRI, and subtle demyelinating feature in the PNS. Work up was negative for common leukodystrophies, but a VUS in TUBB4A was identified by whole exome sequencing. Although associated with hypomyelinating leukodystrophy, to our knowledge, TUBB4A has not been associated with hypomyelination involving both the CNS and PNS. We present a putative novel mutation that suggests that expands the spectrum of TUBB4A associated disorders. More studies are needed to better understand the genotype-phenotype correlations in TUBB4A-associated disorders.

128. Genetic Risk for Elevated BP Predicts 6-Month Blood Pressure Levels after Intracerebral Hemorrhage

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Background: Inadequate blood pressure (BP) control after intracerebral hemorrhage (ICH) is common and associated with increased risk for ICH recurrence and cognitive decline. Identifying patients at the time of ICH hospitalization who are at increased risk for long-term uncontrolled BP post-ICH could improve early intervention to maintain BP control. We investigated whether genetic factors associated with BP levels in large independent populations could help identify patients at increased risk for uncontrolled BP after ICH.

Methods: Subjects were selected from consecutive patients aged ≥ 18 years with CT-confirmed ICH recruited prospectively for a single-center longitudinal study at Massachusetts General Hospital from July 1994 to December 2015. Inclusion criteria were survival >90 days, available genome-wide genotyping data, and available 6-month BP data. Our primary outcome was uncontrolled BP at 6 months (BP ≥ 140/90 mmHg). We constructed a polygenic risk score (PRS) aggregating the effect of independent (r^2<0.4) highly significant ($p<10^{-8}$) common variants associated with SBP from previously published independent GWAS of BP traits. We

examined the association between this PRS and uncontrolled BP in univariate and multivariate models, after adjusting for pre-existing history of hypertension and admission BP at time of ICH.

Results: 169 patients were available for analysis; 82 (48.5%) were male, 157 (92.9%) were white; median age was 71 (IQR, 62-79) years. At 6 months, 96 (56.8%) patients had uncontrolled BP; in the uncontrolled group, median SBP was 144.5 (IQR, 142-149) mmHg and median DBP was 82 (IQR, 78.8-84) mmHg. The BP PRS was associated with increased admission SBP levels (β=8.46 mmHg per 1 SD increase; SE 2.55; p=0.001). There was a suggestive association of the SBP PRS with 6-month uncontrolled BP status (OR 1.32 per 1 SD increase; 95% CI: 0.97-1.82; p=0.08), which persisted and was strengthened after inclusion of pre-existing hypertension and admission SBP in the multivariate model (OR 1.40 per 1 SD increase; 95% CI: 1.01-1.99; p=0.048). Modelling of post-ICH uncontrolled BP status was improved with inclusion of the SBP PRS, compared to clinically relevant BP traits alone (Akaike information criterion 231.59 vs 229.68, likelihood ratio 0.048).

Conclusion: Despite a small sample size, our SBP PRS associates with uncontrolled BP levels after ICH after adjusting for other predictors. Larger sample sizes of sufficient power are required to refine effect size estimates and determine optimal PRS cutoffs for prioritized BP interventions.

129. Leber's Hereditary Optic Neuropathy (LHON)-Like Syndrome in Heteroplasmic Mitochondrial Mutations

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Introduction: Leber's Plus syndromes have been well described in the literature. Intriguingly, an opposite effect occurs when heteroplasmy with more severe mitochondrial mutations present with an LHON-like visual loss at a later age of onset. The small, unmyelinated papillomacular bundle fibers are selectively affected first in these heteroplasmic mitochondrial mutations.

Methods: Case report.

Results: 20-year-old woman with subacute bilateral sequential visual loss (counting fingers at 2 feet OD; 20/400+1 OS, no relative afferent pupillary defect; central scotoma OU; temporal disc pallor OU; superior, temporal, and inferior retinal nerve fiber layer thinning; diffuse ganglion cell layer/ inner plexiform layer thinning OU) presented with an LHON-like syndrome with a non-LHON mutation, a pathogenic variant in MT-ND3 m.10197G>A (p. Ala47Thr) with 51% heteroplasmy. Although MRI of the brain revealed restricted diffusion in the posterior putamens bilaterally, no dystonia or other neurological deficits were present. Idebenone 900 mg/day and vitamin C 500 mg/day resulted in mild visual improvement.

Conclusion: We hypothesize that an LHON-like presentation can be a form fruste of more severe heteroplasmic pathogenic mitochondrial mutations at a later age of onset, irrespective of the mitochondrial DNA (mtDNA) mutation type. Other factors can play a role in the clinical phenotype, including DNA haplotype, nuclear genetic background, environmental factors, etc. Although the mtDNA 10197G>A mutation has been associated with Leigh syndrome, LHON and dystonia (LDYT), and MELAS/LS overlap syndrome (Leng Y., et al., Mitochondrial DNA 2015), our patient had only LHON-like visual loss at the onset of presentation. Another heteroplasmic mtDNA variant of MT-ND1 m.38907G>A, typically causing Leigh syndrome, was shown to have a similar phenomenon of LHON-like visual loss at initial onset. In all cases, the papillomacular bundle is most vulnerable to oxidative damage (Pan, B.X., et al., IOVS 2012). Although these mtDNA mutations affect different ND subunits of complex I, some electrons seem to be transferred through a parallel pathway to complex II, as shown in cybrid studies (Caporali, L., et al., Biochem Biophys Acta 2013).

130. Investigation of *RFC1* Expansions in Sporadic ALS

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Amyotrophic lateral sclerosis (ALS) is an invariably fatal neurodegenerative disease characterized by the progressive degeneration of upper and lower motor neurons in the brain and spinal cord. The large majority of ALS patients do not have a family history of disease, and the genetic etiology of only 10% of these sporadic ALS cases is known. A pentanucleotide repeat expansion within the *RFC1* gene was recently described as a common cause of the cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS). Given the clinical overlap between ALS and CANVAS, and the importance of other repeat expansions in the pathogenesis of ALS, our study aimed to examine the role of *RFC1* repeat expansions in patients diagnosed with sporadic ALS. We examined 1069 clinically diagnosed sporadic ALS patients and 853 neurologically-healthy control participants, using a workflow comprised of short-range PCR, long-range PCR, repeat-primed PCR and Sanger sequencing to identify individuals who carry expansions in *RFC1*. Chi-squared tests with Bonferroni correction were used to compare expansion frequencies between cohorts. The reference $[AAAAG]_{11}$ sequence was observed in the vast majority of ALS and control samples and did not differ between both cohorts (97.1% and 95.7% respectively, p=0.37). The homozygous [AAGGG] expansion previously identified as causative for CANVAS was not observed in any ALS cases or control subjects. However, we observed compound heterozygotes, as [AAAGG]/[AAGGG], in two ALS cases, and this genotype was not observed in control subjects. Several other homozygous repeat expansions were also identified, including $[AAAGG]_{exp}$, $[AAGAG]_{exp}$, and $[AAAGGG]_{exp}$, at low frequencies in cases (0.2%, 0.1% and 0.4% respectively), and mostly absent in controls (0%, 0%, and 0.1% respectively). Though ALS and CANVAS patients both suffer from

neurologic deficits, *RFC1* expansions do not appear to be a shared genetic etiology. However, the *RFC1* locus is pleomorphic, and future studies are warranted.

Neuromuscular Disease

360. Neuropathy-Causing TRPV4 Mutations Disrupt TRPV4-RhoA Interactions and Impair Cytoskeletal Regulation

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A common and longstanding enigma in human genetics, especially of neurodegenerative diseases, is how different mutations in the same gene can result in distinct diseases. Disease-causing mutations in TRPV4 (transient receptor potential vanilloid 4) represent a striking example of such tissue-specific pathology. Dominant missense mutations in TRPV4 cause a spectrum of peripheral nerve diseases including Charcot-Marie-Tooth (CMT) disease and spinal muscular atrophy, while distinct mutations cause connective tissue diseases including skeletal dysplasias. TRPV4 is a plasma membrane-expressed, calcium-permeable cation channel that can influence cytoskeletal changes and cell morphology. Importantly, TRPV4 mutations causing peripheral neuropathy predominantly localize to the intracellular N-terminal domain, whereas skeletal dysplasia mutations occur in multiple regions of TRPV4. Using an unbiased screen, we identified the cytoskeletal remodeling GTPase RhoA as a TRPV4 interactor. We show that TRPV4-RhoA binding occurs via the TRPV4 N-terminal domain, resulting in suppression of TRPV4 ion channel activity, inhibition of RhoA activation, and neurite extension. Remarkably, neuropathy mutations, but not skeletal dysplasia mutations, disrupt TRPV4-RhoA binding, leading to failure of TRPV4 inhibition, excessive RhoA activation, and impaired cytoskeletal outgrowth. Furthermore, inhibition of RhoA can restore neurite length *in vitro* and in a *Drosophila* model of TRPV4 neuropathy. These results highlight both ion channel-dependent and ion channel-independent roles for TRPV4-RhoA interactions in regulating cytoskeletal dynamics and demonstrate multifaceted disruption of TRPV4-RhoA signaling by neuropathy mutations. Thus, dysregulation of TRPV4-RhoA interactions may be a critical determinant of tissue-specific toxicity in TRPV4 neuropathy.

361. Myasthenia Gravis: From Early Descriptions to Early Treatments

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Introduction: Myasthenia gravis (MG) is nowadays a disease with a distinctive clinical presentation and multiple effective treatment options. However, the condition was not fully recognized until the late 19th century and initial treatments only became available in the first half of the 20th century.

Objective: To review the early clinical descriptions and treatments of MG.

Methods: Review of historical documents and other articles related to the history of MG.

Results: Thomas Willis is credited with the first description of MG in 1672, although his contribution went unnoticed until 1903. He called MG "The Spurious Palsy". Other cases probably preceded this description, including the Powhatan chief Opechankanough. In 1877 Samuel Wilks reported a case of bulbar paralysis without pathologic changes in the medulla. Two years later Wilhlem Erb published the first paper entirely dedicated to MG, a description of 3 cases of what he called "A new probably bulbar symptom-complex". He noted the extraocular muscle involvement and was the first to separate the condition from progressive bulbar palsy. In 1893 Samuel Goldflam provided a complete account of MG to date and proposed that it was a curable disease. Friedrich Jolly coined the term "Myasthenia gravis pseudoparalytica" in 1895. Despite being a combination of Greek and Latin words, this terminology stood the test of time. The association between MG and the thymus was first recognized by Leopold Laquer and Carl Weigert in 1901, when they found a thymic lymphoma in the autopsy of a fatal case. Additional studies by E. Farquhar Buzzard, Elexious Bell, Gordon Holmes and Edgar Hughes Norris, supported this association. Ernst Ferdinand Sauerbruch performed the first thymectomy for MG in 1911. Alfred Blalock improved the surgical technique and by 1944 had performed 20 successful operations. Multiple non-surgical treatments were tried without success until 2 astute women made their mark in the history of MG. Harriet Edgeworth, who had MG, reported her own experience with ephedrine in 1930. In 1934 Mary Walker described the beneficial effect of physostigmine, in what became known as "The Miracle at St. Alfege's".

Conclusions: Long after the initial clinical description by Thomas Willis, the characterization of MG evolved with the work of Wilks, Erb and Goldflam. Friedrich Jolly gave MG its name in 1895. Alfred Blalock and Mary Walker were pioneers in the use of thymectomy and cholinesterase inhibitors, which remain mainstays of the treatment of MG.

362. Chemically Patterned Hydrogel Scaffolds Provide Cell-Assembled Matrices to Guide Spinal Cord Regeneration

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Damage to the extracellular matrix (ECM) following spinal cord injury (SCI) contributes to loss of neurologic function.

ECM formed after SCI is biologically primed towards damage containment, and actively excludes neuronal outgrowth and reconnection. We are developing a tissue-engineering strategy which combines hydrogel scaffolds with cells, ECM protein coatings or decellularized ECM, to restore a native matrix for spinal cord regeneration. Oligo(poly(ethylene glycol) fumarate) (OPF) hydrogel sheets were embossed with ridges and functionalized with a chemically-patterned surface to linearize cell and axon growth. OPF was coated with titanium dioxide (TiO_2) followed by a bisphophosphate layer, producing a cell adhesive self-assembled monolayer of phosphonate (SAMP). TiO_2/SAMP was applied onto the OPF surface in linear stripes using a shadow mask. Optimal spacing of 30 um stripes of TiO_2/SAMP, alternating with 30 um of bare polymer, ensured parallel cell and ECM alignment upon decellularization. OPF sheets self-assembled into a spiral scaffold when hydrated. Mesenchymal stromal cells (MSCs), Schwann cells (SC), or their combination, aligned along the direction of the patterning over 7-days in culture. Fibronectin deposition on the scaffold surface increased when SCs and MSCs were co-cultured over SCs alone. Cell-derived ECM aligned in the direction of the striped pattern. Neurons seeded upon co-cultured cells for 4 days had enhanced attachment and neurite extension along the pattern compared to controls. A pilot study confirmed that spiral OPF scaffolds, with and without laminin coating, supported axonal regeneration following implantation into a T9 complete transection SCI in rats over 4 weeks. Subsequently, 6 groups of 7 female rats underwent a T9 spinal cord transection and were implanted with spiral scaffolds, configured as: 1) OPF hydrogel alone; 2) OPF fully coated with TiO_2/SAMP but without patterning; 3) OPF with TiO_2/SAMP in a 30x30 um striped pattern; 4) OPF with full TiO_2/SAMP and ECM derived from the decellularization of NIH 3T3 cells; 5) OPF with patterned 30x30 TiO_2/SAMP and decellularized NIH 3T3 ECM; and 6) a cylindrical multichannel OPF scaffold with Matrigel. Neurologic recovery was assessed by motor function scoring over 5 weeks. Immunohistochemical analysis of axon counts and ECM content is being compared between groups, and the results will be presented. This study highlights the use of decellularization technologies to deliver a biomimetic architecture of ECM as an SCI repair strategy on bioengineered polymer surfaces.

363. Pediatric Small-Fiber Neuropathy: Presentations, Causes, Outcomes

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Sensory/autonomic axon neuropathy is increasingly diagnosed. Excess firing and axonal degeneration causes sensory disturbances including unprovoked widespread chronic pain and itch, plus exertional intolerance, nausea and orthostatic hypotension (Oaklander, 2019). Prolonged SFN causes deconditioning, emotional distress, disability, and socioeconomic damage, with children affected well into adulthood (Murray, 2020). Adult SFN emerged after 1995 as PGP9.5-immunolabeled skin-biopsy testing developed, but most children still remain undiagnosed and untreated. Small-fiber pathology is increasingly reported in ill-defined chronic-pain conditions. Metanalysis in adult fibromyalgia yielded 45% prevalence of diagnostic biopsies (epidermal neurite densities <5th centile; Grayson, 2019); subsequent 117-patient study documented 63% prevalence including more-proximal sites (Evdokimov, 2019). Despite rare monogenic cases, in many small and 3 large pediatric series (Cook-Norris, 2011; n=32), Oaklander, 2013; n= 41), Görlach, 2020; n=26) dysimmunity is discussed, including >65% response to immunotherapies. We now find 53% prevalence of abnormal lower-leg biopsies in juvenile-fibromyalgia patients (Boneparth A, 2020). Given 2-6% U.S. prevalence of fibromyalgia in schoolchildren (Kashikar-Zuck S, 2014), pediatric SFN could be endemic, prioritizing bioinformatic study of large datasets. NINDS thus requested (R01NS093653, 2NS093653) we develop and adapt adult SFN assessments for children prioritizing age-feasible, remote-accessible metrics. The goal is to characterize presentations, causes, and treatment outcomes to generate pediatric case definitions, diagnostic frameworks and treatment recommendations. With IRB approval, we are compiling and analyzing electronic health records of individuals <18y at first SFN assessment at Massachusetts General Hospital (MGH) and now track >370 participants (>330 patients, 45 healthy age-matched controls). Patient age averages 14.3±3.5y (2.67-17.98y). 66% are female, 4.4% Hispanic, 93.9% Caucasian, 1.1% Asian, 1.4% Black, and 3.6% multiracial/other/unknown. PGP9.5-labeled skin biopsies from patients and controls (>450) comprise 416 from standard lower-leg sites, 45 from thigh, and >75 repeats including >40 simultaneous leg/thigh biopsies and 18 patients with repeat biopsies during treatment. 36% (131) had ≥1 diagnostic lower-leg biopsy, with 8.8% (32) borderline (5^{th}-10^{th} centile). Children/parents complete REDCap on-line adult-validated Small-fiber Symptom Surveys (Treister, 2015), neurologists complete the MAGNET Neuropathy Exam Tool (Zirpoli, 2018) and perform standardized autonomic-function testing. Patients undergo evidence-based blood-test screening for causes (Lang, 2016), plus outcomes of genetic testing and disease-modifying therapies including immunotherapy (Liu, 2018) and precision treatments (e.g., for HSAN-1 (Fridman, 2019)) are tracked. This registry analysis identifies many cases of pediatric SFN, particularly in girls. Despite rare monophasic (Faignart, 2020) and familial presentations (de Greef, 2018), the tempos and recoveries highlight potentially modifiable causes.

364. Brain Strength: Multi-Modal Brain MRI Predicts Grip Strength

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Muscle strength testing is a mainstay of clinical practice and used to identify weakness, a common finding in many neurological conditions. The morphometry and composition of muscles influence force generation — the most visible example being the increase in muscle size, muscle hypertrophy, which accompanies gains in strength. Muscle strength, however, is only partially explained by the muscles, themselves, and adaptions within the nervous system also contribute to strength gains. Here we characterize and quantify the central nervous system's (CNS) contribution to strength by demonstrating the power of MRI-derived brain features to predict grip strength. We obtained multi-modal brain MRI data from the Human Connectome Project's 1200 subjects release, which included dominant hand grip strength measures (NIH Toolbox with hand-held dynamometry) and 3T structural MRI, diffusion MRI, resting-state functional MRI (fMRI), and task-evoked fMRI, providing measures on gray matter, white matter, resting-state functional connectivity, and motor task activation. The data were split into training (n=970, age=28.8±3.7 years, 525 females) and testing (n=75, age=28.5±3.7 years, 38 females) datasets. Within a cross-validation framework, we first systematically evaluated multiple prediction pipelines (80 in total) for each MRI modality using the training dataset. The performance of the optimal prediction pipelines for each modality was then assessed on the independent, testing dataset. Each modality demonstrated predictive power exceeding chance accuracy ($p<0.001$). The resting-state functional connectivity prediction pipeline had the highest performance (MAE=6.18 lbs, RMSE=7.71 lbs, $r^2=0.452$). The gray matter (MAE=6.92, RMSE=8.27, $r^2=0.369$) and white matter (MAE=6.41, RMSE=8.44, $r^2=0.342$) prediction pipelines performed similarly well to each other. The left hand (MAE=8.11, RMSE=9.67, $r^2=0.137$) and right hand (MAE=7.89, RMSE=9.83, $r^2=0.108$) motor task fMRI prediction pipelines had the lowest performance. Next, we combined the prediction pipelines across the modalities into a multi-modal prediction pipeline using a cross-validated stacked regression ensemble. The multi-modal prediction pipeline outperformed the individual modalities explaining more than 50% of the variance in grip strength (MAE=5.98, RMSE=7.18, $r^2=0.523$) and demonstrated no significant bias across the range of grip strength measures or with respect to gender, age, or handedness. We postulate that these MRI-based prediction pipelines can provide complementary, neurobiologically-based measures of neuromuscular function and may prove to have diagnostic value, by helping localize pathology: central versus peripheral and functional versus structural, as well as prognostic and predictive value, where higher predicted grip strength may mean greater CNS capacity for motor recovery following physical or surgical interventions.

365. Using Active Digital Phenotyping to Quantify Function and Cognition in Amyotrophic Lateral Sclerosis

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Background: Amyotrophic lateral sclerosis (ALS) clinical trials employ traditionally accepted outcome measures such as the revised ALS Functional Rating Scale (ALSFRS-R), vital capacity (VC), and handheld dynamometry (HHD). Active digital phenotyping (ADP), in which human phenotype data is gathered during diagnostic tasks that people perform on digital devices, may provide more granular and quantitative measurements of function compared to traditional ALS outcome measures. Active digital phenotyping may also enable assessment of cognition in ALS. To understand, select, and develop digital ALS outcome measures, we aim to collect and analyze ADP data alongside traditional outcome measures in people with ALS (PALS) and controls.

Methods: The study consists of two in-person visits separated by approximately one week. At each visit, participants complete traditional ALS outcome measures and active digital phenotyping tasks: 1) tests of executive function on a tablet-based platform (TabCAT), 2) movement quantification using accelerometers and gyroscopes (gross motor) and a computer mouse (fine motor), and 3) mobile tasks of gross/fine motor function and cognition using an Apple Watch and iPhone (completed in-clinic and at-home).

Results: Eight participants have completed the study (6 ALS and 2 control). Multiple computer mouse task features have a test-retest reliability > 0.8 and correlate well ($r > 0.8$) with at least one of the relevant ALSFRS-R questions or muscle strength recordings. These features include movement time, click duration, execution time, movement direction changes, and normalized jerk. On TabCAT, the Social Norms Questionnaire (SNQ) shows a test-retest reliability of >0.9 and correlates with ALSFRS-R total score ($r=0.84$). iPhone-based alternating finger tapping is also reduced in PALS and associated with ALSFRS-R fine motor scores. Updated data will be included in the presentation.

Conclusion: This study will help define the utility of a variety of active digital phenotyping tools in ALS, compare these tools to traditional ALS outcome measures, and extend our ability to assess cognition in PALS. Early results suggest at least a subset of the active digital phenotyping tests in this study have promise as reliable measurements of function and cognition in PALS.

366. *DNAJB6* Isoform Switching: Mechanistic Insights and Therapeutic Potential for Limb Girdle Muscular Dystrophy 1D

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Dominant missense mutations in DNAJB6, a ubiquitously expressed HSP40 co-chaperone cause limb girdle muscular dystrophy (LGMD) 1D, an adult onset slowly progressive myopathy with vacuolar and aggregate myopathology. Treatments for dominant LGMDs require a customized approach

and have lagged behind recent advances in gene transfer strategies for many recessive LGMDs. DNAJB6's role in LGMD1D pathogenesis is increasingly thought to result from DNAJB6b, a short isoform that localizes to Z discs and myonuclei in skeletal muscle. DNAJB6a, a nuclear predominant isoform, has higher expression levels in mature skeletal muscle, yet is not thought to contribute to LGMD1D pathogenesis. Current mechanistic data is conflicting regarding a toxic gain of function, a dominant negative mechanism, or even a combination of both. We have developed an antisense oligonucleotide approach to titrate DNAJB6 isoform switching. Modulating DNAJB6 isoform levels in *knock-in* LGMD1D mice will clarify each isoform's contribution to disease pathogenesis and may have therapeutic potential as well.

367. When a Neuropathy Doesn't Rhyme, it Could be POEMS Syndrome

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Introduction: During evaluation of a rapidly progressive neuropathy with a plasma cell disorder, chronic inflammatory demyelinating polyradiculoneuropathy, multiple myeloma, plasmacytoma, monoclonal gammopathy with undetermined significance, , amyloidosis, cryoglobulinemia, waldenstorm macroglobulinemia and POEMS syndrome should be explored. POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal proteins, Skin changes) syndrome is characterized by monoclonal plasma cell disorder, polyneuropathy and one or more of the following features: osteosclerotic myeloma, Castleman's disease, increased levels of vascular endothelial growth factor (VEGF), organomegaly, endocrinopathy, edema, typical skin changes and papilledema.

Case Summary: 59-year-old lady presents with subacute onset and rapidly progressive paresthesias and weakness in the lower followed by upper limbs. She had severe sensory deficits in the form of impaired vibration, proprioception and pin prick sensation with complete areflexia. She had Medical Research Council (MRC) grade 3/5 strength in lower and upper limbs. Nerve conduction studies and electromyography reported severe sensorimotor axonal polyneuropathy with additional features of demyelination. Immunofixation electrophoresis showed IgG lambda monoclonal restriction. CT scan of the chest, abdomen and pelvis showed many osseous sclerotic lesions in the thoracic and lumbar vertebral bodies and sacrum. There was moderate four-chamber cardiomegaly. Whole body positron emission tomography showed large lytic lesions in the right hemisacrum (3.4 cm x 2.7 cm x 3.9 cm) and at the posterior right acetabulum (rounded 9 mm) with abnormal hypermetabolic activity. Complete blood count showed severe thrombocytosis (platelets >650,000/cubic millimeter). MRI of the lumbar spine showed a diffuse abnormal enhancement of the cauda equina nerve roots concerning for a leptomeningeal carcinomatosis. Based on the presence of polyneuropathy, mild cardiomegaly, IgG lambda gammopathy, osseous sclerotic bone lesions and thrombocytosis, a diagnosis of POEMS syndrome was suggested. Further evaluation showed severely elevated VEGF at >700 picogram/milliliter (normal <96.2 picogram/milliliter) Biopsy of the right sacral mass suggested a plasma cell neoplasm. She was started on lenalidomide chemotherapy for the neoplasm.

Conclusion: A chronic overproduction of proinflammatory cytokines appears to be a major feature of POEMS syndrome. With regards to treatment, patients with less than three bone lesions are best managed with radiotherapy to eliminate the source of the disease. For the rest, autologous stem cell transplant (ASCT) is very effective. Lenalidomide may also be used either first- or second-line treatment. Plasma exchange and IVIG have been shown to be ineffective.

368. Futility of Intravenous Immunoglobulins in a Subset of Lower Motor Neuron Syndromes

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Objective: We aimed to explore utility of intravenous immunoglobulin (IVIG) in patients with pure lower motor neuron syndromes with no conduction block on neurophysiological studies and absence of any ganglioside antibodies.

Background: IVIG use, common in pure lower motor neuron syndromes, may not have rational utility in some subsets.

Design/Methods: We studied six consecutive patients presenting with a progressive pure lower motor neuron syndrome in a six-month period. Mean age was 60.1 years with 3 females and 3 males. No patient had any bulbar, respiratory or sensory dysfunction or any limb muscle atrophy. Four patients received IVIG for 3 months, one patient for 7 months and one patient for 12 months. Neurology exam was periodically documented on each clinic visits using the Medical Research Council (MRC) scoring system.

Results: Of the 4/6 patients who received IVIG for a short duration of three months, 3 had unchanged neurology exam and 1 patient had evolution of new weakness in a different limb. Of the 2/6 patients who received IVIG for a slightly longer period (7 months and 12 months), both had unequivocal progression of weakness.

Conclusion: Lower motor neuron syndromes often have slower progression. While being treated with IVIG, if analysed only over a short period of time , it may give a false perception of disease stabilization. A placebo response based on subjective improvement is also an additional confounding factor that unnecessarily promotes long term use of IVIG in this patient population. In reality, most of these patients without any conduction block on neurophysiology studies and absence of serum IgM GM1 antibodies continue to slowly decline on long term follow up. We propose that an actual improvement in muscle strength rather than just

disease stabilization is a better clinical marker to analyse effectiveness of IVIG.

369. Longitudinal Study of Cognitive and Behavioral Impairments in the Veteran ALS Population

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Introduction: Amyotrophic lateral sclerosis (ALS) is an incurable progressive neurodegenerative disease that predominantly causes irreversible motor symptoms. However, ALS can also lead to cognitive and behavioral impairments that are characterized by personality changes and deficits in frontal executive tests. Moreover, ALS and frontotemporal dementia have been shown to overlap clinically, pathologically, radiologically, and genetically. Little is known about the longitudinal course of these behavioral and cognitive impairments in ALS.

Objective: To determine the longitudinal course of cognitive and behavioral impairments in Veterans with ALS through the use of the ALS Cognitive and Behavioral Subscales (ALS-CBS) and selected MOCA sections.

Method: A retrospective chart review was conducted. ALS-CBS, selected MOCA sections, and the ALSFRS-R were administered to 34 ALS patients followed in the VA GLA ALS Multidisciplinary Clinic from 2016 to 2020. Patient scores on the ALS-CBS, selected MOCA sections, and ALSFRS-R were evaluated for all patients throughout their treatment.

Results: The initial mean score on the ALSFRS-R was 31/48. The initial mean score on the ALS Cognitive Subscale was 11/20 and on the ALS Behavioral Subscale was 32/45. The average rate of decline over 6-month intervals on the ALSFRS-R was 2.89. The average rate of decline on the ALS Cognitive Subscale and ALS Behavioral Subscale were 0.17 and 3.11, respectively. The R^2 value when the ALSFRS-R average scores were plotted against the ALS Cognitive Subscale average scores was 0.01. The R^2 value when the ALSFRS-R average scores were plotted against the ALS Behavioral Subscale average scores was 0.6. The MOCA visuospatial/executive subscale showed an average 6-month decrease of 0.67.

Conclusion: These data suggest that Veterans in our ALS cohort presented initially with significant impairments in both cognition and behavior. Patients' cognitive subscale scores continued to decline at a mild rate but did not develop into FTLD cognitive type. The patients' ALS Behavioral Subscale declined at a more rapid rate with a majority developing possible FTLD behavioral type. Moreover, the R^2 values suggest that motor impairments do not influence cognitive decline but may play a role in the behavioral decline or vice versa. The decrease in MOCA visuospatial/executive subscale reflects frontal and parietal lobe neurodegeneration. More research must be done to improve our understanding of cognitive and behavioral impairments in ALS to allow us to improve care for patients and their families.

370. Characterizing the Histological and Behavioral Phenotypes of a Humanized Knock-In Mouse Modeling a Deep Intronic Mutation in Collagen VI-Related Dystrophy

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Collagen VI is an extracellular matrix protein. A common and recurrent dominant negative deep intronic C>T mutation in the *COL6A1* gene inserts a 72-nucleotide-long pseudoexon between exons 11 and 12 in 50% of the mutant allele transcripts. Patients carrying this mutation experience early-onset muscle weakness, joint contractures, and respiratory insufficiency. As mouse and human intronic sequences are nonhomologous, we have generated a humanized knock-in mouse model carrying either the wild type (HumC) or mutant (HumT) alleles in order to investigate this variant's pathophysiology and to test splice-correction therapies *in vivo*. Here, we comprehensively characterized the phenotype of this new model and identified outcome measures that will enable assessing the efficacy of therapeutic interventions in rescuing phenotype. Grip strengths of male (M) and female (F) $Col6a1^{+/+}$ (n= 9M, 9F), $Col6a1^{+/HumC}$ (n= 8M, 7F), $Col6a1^{HumC/HumC}$ (n= 3M, 4F), $Col6a1^{+/HumT}$ (n= 9M, 9F), $Col6a1^{HumT/HumT}$ (n= 6M, 5F) mice were measured monthly from postnatal day (PND) 28 to PND 140. The mice were weighed every 2 days from PND 14 to PND 42, then weekly to PND 140. Muscles from 11-month-old $Col6a1^{+/+}$, $Col6a1^{+/HumC}$, and $Col6a1^{+/HumT}$ mice were stained with hematoxylin and eosin, and immunohistochemically stained for collagen VI and laminin. For 2-month-old males and 4-month-old females, the average grip strengths of $Col6a1^{+/HumT}$ and $Col6a1^{HumT/HumT}$ mice were significantly weaker than those of all other genotypes ($p<0.05$). However, there was no statistically significant difference in weight or percent weight change. The preliminary histological data showed that $Col6a1^{+/HumT}$ quadriceps had more central nuclei than the other genotypes' quadriceps. Additionally, among the $Col6a1^{+/HumT}$ muscles, the tibialis anterior and quadriceps muscles had more central nuclei than the extensor digitorum longus, gastrocnemius, soleus, and triceps muscles. Our findings suggest that central nuclei quantification and grip strength measurement could be appropriate outcome measures to assess the efficacy of human-ready antisense drugs in this humanized knock-in *Col6a1* mouse model.

371. Heat Sensitivity in Lou Gehrig's Disease

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Background: Uhthoff's phenomenon, transient exacerbation of underlying demyelinating neurological disease in response to elevated body temperature, has been described exclusively in a variety of white matter diseases, including multiple sclerosis (Opara, 2016). This may be due to delay or block in axonal conduction (Froman, 2013). Presence of Uhthoff phenomena in disorders of ventral horn cells and white matter, such as Amyotrophic Lateral Sclerosis (ALS), has not heretofore been reported. Such a case is presented.

Methods: Case study: A 71-year-old right-handed woman presented with a two year course of progressive reduction in strength involving both hands, shortness of breath upon exertion, difficulty walking, and nocturnal muscle spasms. After bathing in steam sauna treatment, she experienced immediate fatigue, worsening weakness, inability to walk along with worsening shortness of breath, which would last as long as a week. This would reoccur after each sauna treatment. When she discontinued use of the steam sauna, the exacerbation of weakness resolved.

Results: Abnormalities in Physical examination: Neurological Examination: Cranial Nerve (CN) Examination: CN XII: Fasciculation of tongue with percussion myotonia of the tongue. Motor examination: Bulk: atrophy in bilateral thenar and hypothenar eminences and intrinsics. Percussion induced fasciculation and myotonia. Strength: intrinsics 4/5 in both upper extremities, 3/5 in bilateral abductor pollicis brevis, 3/5 right gastrocnemius and soleus. Gait: Heel and toe unstable with circumduction of left leg. Reflexes: 1+ left brachioradialis. 1+ left triceps. 3 + bilateral knee jerks. 0 left ankle jerk. Positive jaw jerk. EMG: fibrillation, positive wave and fasciculation in all four extremities, MRI of brain and spinal cord: hyperintense T2 flair in bilateral corticospinal tracts, left greater than right in the brain.

Discussion: The mechanism of Uhthoff's phenomenon in this individual may be an exacerbation of destruction causing dysfunction of the pathological white matter tracts of the corticospinal system, as opposed to impact upon the anterior horn cells. In Uhthoff's phenomenon, there may be a transformation of nerve conduction from saltatory to continuous conduction due to conduction blockade (Frohman, 2013). Given the above, it may be prudent to suggest those with Lou Gehrig's disease should avoid sauna hot baths or excessively hot bathing.

372. Dietary Weight Loss May Halt Progression of Polyneuropathy in Patients with Obesity

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Recent studies highlight obesity as an important risk factor for polyneuropathy. The objective of this study was to explore the effect of medical weight loss on polyneuropathy outcomes. We analyzed data from a prospective cohort undergoing medical weight loss in a specialized clinic at the University of Michigan. Weight loss was achieved by providing participants with very low calorie diets (VLCD) in the form of meal replacement (800 kcal/day) for 12 weeks and then slowly transitioned to 1200-1500 kcal/day. The co-primary outcomes were change in intraepidermal nerve fiber density (IENFD) in the thigh and distal leg. Secondary outcomes included nerve conduction studies, Michigan Neuropathy Screening Instrument (MNSI) questionnaire and exam, short-form McGill pain questionnaire, NeuroQoL, and quantitative sensory testing (QST). Among 120 patients enrolled in the IWMC study, 72 (mean [SD] age: 50.10 [10.47, 36 Females, 63 whites) completed 2 years of follow-up. Patients lost 12.38 kg [11.83] (10.25 % weight reduction). All metabolic syndrome components improved with the exception of blood pressure. IENFD in the thigh (0.05 [1.19], p=0.73) and distal leg (0.14 [1.03], p=0.32) did not significantly change. Improvements were observed on the MNSI Questionnaire: -0.59 [1.43], p <0.01; two NeuroQoL components (Pain: -0.35 [1.14], p = 0.01; and Emotional: -0.71 [2.2], p =0.01), and QST cold -1.93 [5.34], p<0.01. No significant changes were observed in other secondary outcomes. Medical weight loss was associated with improvements in all metabolic parameters other than blood pressure, and both IENFD outcomes remained stable after 2 years. Given that natural history studies reveal decreases in IENFD over time, medical weight loss may halt this progression, but randomized controlled trials are needed. Uncontrolled exercise interventions revealing improvements in IENFD may indicate that exercise as greater effects than medical weight loss, but comparative effectiveness clinical trials are required. Encouragingly, four secondary polyneuropathy outcomes revealed improvements after medical weight loss, but NCS, MNSI examination, and the short-form McGill pain questionnaire remained unchanged.

373. Home-Based Teleyoga Breathing Meditation in Patients with ALS

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Introduction: While non-invasive mechanical ventilation has been shown to help prolong survival and slow respiratory decline in ALS patients, more therapies focused on preserving respiratory function are needed. In patients with emphysema, yoga breathing was found to have a beneficial effect on respiratory parameters, exercise tolerance and dyspnea-related anxiety. We studied the feasibility of teleyoga breathing meditation in patients with ALS and its effects on pulmonary function and quality of life measures.

Method: This was a non-randomized pilot study that included 11 ALS patients. Subjects completed 9 weekly online group sessions of yoga breathing via Zoom video conferencing with a certified yoga instructor. Adherence rates, acceptability of the intervention and technical issues were recorded. Secondary outcome measures included the forced vital capacity (FVC), ALS functional rating scale, modified Borg dyspnea scale and Short-Form 36 survey.

Results: Of 11 patients who entered the study, 7 (5 women, 2 men) participated in the active intervention. The practice was well tolerated with no adverse effects and

was rated favorably by participants. Although the study was not powered for efficacy and no significant changes were seen in clinical outcome measures due to small sample size, the average decline in upright FVC was -0.02L per month (95% CI -0.15, 0.10) and average decline in percent-predicted FVC was 0 (95% CI -1.7, 1.7).

Conclusion: Yoga breathing in ALS patients is a safe and feasible practice with high adherence rates and acceptability ratings. Potential benefits may be related to the slow relaxed breathing practice, which may help with anxiety and result in longer expiration times and reduced CO2 retention. In addition, the home-based program allows for ease of practice and scalability to the general ALS population.

374. Overview of the Healey Center's Expanded Access Programs for Investigational Treatments in Amyotrophic Lateral Sclerosis

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Expanded access protocols (EAPs) occupy a space between more formal clinical research trials and routine clinical care. They provide patient access to experimental treatments in clinical development that could provide therapeutic benefit and are unavailable through standard clinical care or ongoing traditional clinical trials. For example, people with advanced ALS are often excluded from ALS clinical trials, which focus on evaluating the impact on early disease trajectory. EAPs can also provide useful data on safety and treatment-related biomarkers that can be utilized for drug development. Additionally, EAPs may create a pre-existing market demand which can be utilized by drug manufacturers if their investigational treatment is approved. The creation and maintenance of a successful EAP program requires the study team to build and sustain a complex relationship between many parties: the patient, the treating physician/principal investigator, an industry or academic drug development partner, an institutional review board (IRB), and the FDA. EAPs can be divided into three broad categories: individual patient use, intermediate-sized population, and widespread (large patient population) use. The Healey Center for ALS at Massachusetts General Hospital currently manages eight expanded access protocols. These include four single-patient and four intermediate-sized protocols, with a total of six different investigational therapies. From July 2018 to March 2020, 57 people with ALS have enrolled across all of the Healey Center's EAPs, with an average age of 58 years old. 43 of these participants were male and 14 were female. Average time from symptom onset to diagnosis was 13 months, and from symptom onset to screening was 41 months. Site of ALS symptom onset was limb for 39 patients and bulbar for 18 patients. FDA approval took approximately 37 days following submission (for those INDs held by the Healey Center at MGH) and IRB approval took approximately 40 days. The average monthly cost of EAPs, per participant, ranged from $746 to $848 over the past three months. These costs include staffing, data management, supplies, and facility use. Philanthropic donations to the Center cover these costs. Sharing our experience may help other academic centers to establish EAPs. Furthermore, innovations in virtual visit follow-up and approaches to ease participant burden in our EAP programs may prove to be helpful for trials in ALS and other neurological disorders.

375. Rationale and Design of Neuro-Ttransform, a Phase 3 Study to Evaluate the Efficacy and Safety of AKCEA-TTR-LRx (ion-682884) in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy (hATTR-PN)

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Background: hATTR-PN is a progressive and fatal sensorimotor and autonomic polyneuropathy caused by misfolding and systemic aggregation of transthyretin (TTR). Inotersen (Tegsedi™) is an approved antisense therapeutic that inhibits TTR production. AKCEA-TTR-L_{Rx} shares the same oligonucleotide sequence as inotersen but is conjugated to a triantennary N-acetyl galactosamine moiety for receptor-mediated delivery to hepatocytes, the principle site of TTR production. A phase 1 study of AKCEA-TTR-L_{Rx} showed 45 mg every 28 days (~$1/27^{th}$ the monthly exposure of inotersen) produced a maximum mean reduction of 86% from baseline in serum TTR levels after 4 doses (before steady state is reached).

Objective: NEURO-TTRansform (NCT04136184) is a phase 3 global, open-label, 80-week study that aims to determine safety and efficacy of AKCEA-TTR-L_{Rx} compared to a historical placebo-control group for the treatment of hATTR-PN.

Methods: 140 hATTR-PN patients will be randomized to receive either AKCEA-TTR-L_{Rx} (n = 120; 45 mg subcutaneously (SC) every 4 weeks) or inotersen (n = 20; 300 mg SC weekly). Patients receiving inotersen will be crossed over to AKCEA-TTR-L_{Rx} after 35 weeks. Key inclusion criteria mirror those of NEURO-TTR and include preserved ambulatory status (Familial Amyloid Polyneuropathy or FAP stage 1 or stage 2), confirmed TTR mutation, and Neuropathy

Impairment Score (NIS) between 10 and 130. Key exclusion criteria include platelets ≤ 125×10^9/L, estimated glomerular filtration rate < 45 mL/min/1.73 m^2, and urine protein/creatinine ratio ≥ 1000 mg/g. Concomitant treatment with inotersen or patisiran are not allowed. Prior treatment with tafamidis, diflunisal, doxycycline or tauroursodeoxycholic acid must be discontinued ≥ 2 weeks prior to first dose. Co-primary efficacy endpoints at Week 66 are change from baseline in serum TTR concentration, modified NIS+7, and Norfolk Quality of Life-Diabetic Neuropathy. An interim analysis will be performed at Week 35. Secondary endpoints include the change from baseline in the Neuropathy Symptom and Change Score, Physical Component Summary score of 36-Item Short Form Survey, Polyneuropathy Disability Score, and Modified Body Mass Index.

Results: This trial is currently enrolling patients.

Conclusions: Despite recent advances, there is still a need for effective, well-tolerated and convenient treatments for hATTR-PN. NEURO-TTRansform is a trial designed to evaluate the efficacy and safety of AKCEA-TTR-L_{Rx}, which, with higher potency and monthly dosing, offers the potential to improve on currently available therapies for hATTR-PN.

376. Historical Perspective of Lambert Eaton and Rooke, Myasthenic Syndrome

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Objective: To provide a historical perspective to the evolution of a presynaptic myasthenic syndrome currently known as Lambert Eaton syndrome (LEMS), as originally described by Edward Lambert, Lee Eaton, and Douglas Rooke.

Background: Edward Howard Lambert is one of the icons of neurology, whose work in neuromuscular electrodiagnostic studies established it as one of the most sought subspecialties in neurology. He along with Lee McKendree Eaton and Edward Douglas Rooke helped identify a unique myasthenic syndrome, known to be associated with pulmonary malignancy.

Design/Methods: Data was collected from library and Internet resources at UCLA and archives at Mayo Clinic, Rochester, Minnesota.

Results: The trio described the very special symptomatology in their groundbreaking abstract in the American Journal of Physiology titled "Defect of neuromuscular conduction associated with malignant neoplasm". Subsequently, Lambert performed specialized electro-diagnostic testing that was characterized by marked incremental responses with high frequency repetitive nerve stimulation. The historic article written and titled "Electromyography and Electric Stimulation of Nerves in Diseases of the Motor Unit" by Eaton and Lambert was published in the Journal of the American Medical Association in 1957. The clinical and electro-diagnostic findings described by these neurologists distinguished LEMS from myasthenia gravis and provided an electrophysiological criterion that served as a foundation for the diagnosis of this syndrome. The disease initially named Eaton Lambert Rooke syndrome, was later known as Eaton-Lambert syndrome. With changing times, the name was modified as the Lambert-Eaton myasthenic syndrome. Additional studies showed that antibodies with specificity for P/Q-type calcium channels were involved in the pathophysiological process of LEMS. These studies opened the doors to various forms of treatments to this disorder including immunotherapy. Despite the fact that our knowledge about LEMS has expanded exponentially, the core foundation lies in the article published by Lambert and Eaton in 1957. Later, other forms of non-paraneoplastic LEMS were also described.

Conclusions: Lambert, Eaton and Rooke identified a unique myasthenic syndrome that can be associated with malignancy. They also described techniques of electromyography, its use and effectiveness in the diagnosis and study of diseases of the motor unit (neuromuscular diseases). We aim to emphasize the historical perspectives that led to the discovery of this unique myasthenic syndrome.

377. Myotonic Dystrophy Phenocopies Sleep Features of Idiopathic Hypersomnia

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Introduction: Myotonic Dystrophy type 1 (DM1), a multisystem, autosomal-dominant disease, is the most common adult muscular dystrophy. Excessive daytime sleepiness is a pernicious, non-muscular symptom for which the cause and treatment remain enigmatic.

Methods: DM1, idiopathic hypersomnia (IH), and non-sleepy controls completed short-form Beck Depression Inventory (BDI), Epworth Sleepiness (ESS), Multidimensional Fatigue Inventory (MFI), Fatigue Severity (FSS), Horne-Ostberg, Functional Outcome of Sleep (FOSQ), Hypersomnia Severity (HSI), and Sleep Inertia (SIQ) questionnaires and underwent 2-weeks' actigraphy, polysomnography (PSG), multiple sleep latency testing (MSLT), and lumbar puncture. DM1 patients with treatment-refractory EDS underwent treatment with flumazenil, motivated by experiences treating refractory IH.

Results: 12 DM1 (7 men; mean [sd] age 32[12.3]), 16 IH (2 men; age 29[11.8]), and 19 age-matched controls (7 men; age 27.5[6.8], p=0.4 for age) participated. DM1 and IH patients were similar and more negatively impacted than controls by: sleepiness (ESS (15.1[3.6] for IH, 14.2[3.5] for DM1, 6.4[3.6] for controls, p<0.0001), FOSQ (p<0.0001), hypersomnia (HSI; p<0.0001), sleep inertia (SIQ; 12.9[3.7] for IH, 11.5[2.0] for DM1, 7.6[2.3] for controls, p<0.0001), and fatigue (FSS and MFI both p<0.001). DM1 and IH shared an evening chronotype versus controls (p<0.01). Depression did not differ by group. On actigraphy, IH patients slept longer (456[65] min for IH, 429[38] for DM1, 393[64] for controls, p = 0.02). PSG sleep time (p=0.06) and sleep efficiency (p=0.09) did not differ. DM1 patients had mild sleep apnea (AHI 1.1[2.5] for IH, 6.8[5.9] for DM1, 2.0[2.9] for controls, p=0.001). MSLT latencies were similar across groups (9.7[5.6] minutes for IH, 8.0[5.0] for DM1, 11.3[5.2] for controls, p=0.30), as were multiple MSLT sleep-onset REM periods (25% for IH, 40% for DM1, 6% for controls, p=0.08). DM1 patients had lower CSF hypocretin (322.6[56.9] for IH, 265.3[53.0] for DM1,

300.5[50.8] for controls, p=0.049), but none were <110 pg/ml. Seven of 8 DM1 patients reported benefit from flumazenil, with pre-post treatment improvements in ESS (p=0.02), FOSQ (p=0.02), and HSI (p=0.02). One patient discontinued flumazenil due to cost, another preferred modafinil, whereas five patients have continued treatment for months to three years absent adverse events.

Conclusion: DM1 phenocopies EDS in IH which is refractory to conventional treatments. Mimicry in a small group extends to clinically-significant improvements in EDS, sleep-associated quality of life, and hypersomnia with transdermal flumazenil treatment. Mechanistic details and improved diagnostic and outcome methods require additional investigation, given the substantial unmet clinical need.

378. Humoral Immune Endoneurial Microvasculopathy: Treatable Non-Inflammatory Axonal Neuropathies

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Introduction: We studied motor-sensory axonal polyneuropathies with C5b-9 complement deposition on endoneurial microvessels.

Methods: Review of 16 consecutive adults with motor-sensory polyneuropathies and C5b-9 deposition on endoneurial microvessels. Strength was measured using quantitative hand held dynamometry. Treatment was 1 gram intravenous methylprednisolone for 5 consecutive days, and then weekly.

Results: Patients (aged 34 to 83 years; 75% male; 56% diabetic) had progressive (median duration 2 years), asymmetric, distal predominant, weakness and sensory loss in legs ± arms (44%). Electrodiagnostic studies showed axon loss. Nerve biopsies showed C5b-9 deposition on endoneurial microvessels and axon loss, usually varied among fascicles. Patients commonlyimproved in strength after treatment (p = 0.00004).

Discussion: Motor-sensory axonal polyneuropathies with non-inflammatory, humoral immune endoneurial microvasculopathy (HIEM) (C5b-9 deposition) frequently have progressive asymmetric, distal leg ± hand, weakness that improves rapidly after high dose corticosteroid treatment. HIEM may represent a new class of non-inflammatory-vasculopathic, treatable axonal neuropathies.

379. Myositis Associated Anti-NT5C1A Autoantibody in Clinical Practice

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Objective: To define the diagnostic utility and clinicopathologic features correlating with anti-cytosolic 5′-nucleotidase 1A (NT5C1A) antibody positivity in idiopathic inflammatory myopathies (IIMs).

Methods: 4987 patients had anti-NT5C1A antibody status clinically tested between 2014 and 2019 in the Washington University neuromuscular clinical laboratory. Using clinicopathologic information available for 630 of these patients, we classified them as inclusion body myositis (IBM), dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy (IMNM), non-specific myositis, or non-inflammatory muscle diseases.

Results: Anti-NT5C1A antibody was found in 182/287 patients with IBM (63%), 11/53 patients with dermatomyositis (21%), 7/27 patients with antisynthetase syndrome (26%), 9/76 patients with IMNM (12%), 20/84 patients with non-specific myositis (24%), and 6/103 patients with non-inflammatory muscle diseases (6%). The sensitivity and specificity of anti-NT5C1A antibody seropositivity for the diagnosis of IBM was 63% and 85%, respectively. Anti-NT5C1A antibody positive IBM patients had a higher frequency of finger flexion weakness ($p<0.01$) and their biopsies harbored more COX negative fibers ($p=0.04$). 18% of anti-NT5C1A antibody negative IBM patients seroconverted to anti-NT5C1A antibody positive on repeat testing.

Conclusions: This is the largest description of patients tested by a clinical diagnostic lab for anti-NT5C1A antibody. We confirm the sensitivity and specificity of anti-NT5C1A antibody for IBM and identified clinicopathologic features in IBM which correlate with anti-NT5C1A antibody status. Anti-NT5C1A antibody testing increased both the diagnostic sensitivity and specificity of IBM when combined with patient age, gender and creatine kinase level.

380. Accurate Test of Limb Isometric Strength (ATLIS) as an Outcome Measure in Upper Motor Neuron Predominant ALS and Primary Lateral Sclerosis

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Outcome measures in amyotrophic lateral sclerosis (ALS) clinical trials rely mostly on changes in lower motor neuron (LMN) function. Quantitative and sensitive measures of disease progression in upper motor neuron (UMN) predominant ALS or Primary Lateral Sclerosis (PLS) are lacking. Recently, the Accurate Test of Limb Isometric Strength (ATLIS) was validated and shown to be more sensitive than either vital capacity or the revised ALS Functional Rating Scale (ALSFRS-R) but its utility in monitoring disease progression in UMN predominant ALS or PLS is unknown. To evaluate markers of disease progression in UMN predominant ALS and PLS using ATLIS we are analyzing parameters in addition to peak force in this population. These ATLIS parameters include *time to peak force, rate of ascent to peak force, time to maximum rate,* and *time to plateau*. To date, we have enrolled 126 patients diagnosed with motor neuron disease as part of a longitudinal ATLIS study at Cedars-Sinai

Medical Center. Forced vital capacity, ALSFRS-R, and ATLIS scores were obtained longitudinally for most of those patients. A retrospective analysis of the 126 subjects identified 7 patients diagnosed with PLS at the time ATLIS was first performed, 7 UMN predominant ALS patients, and 11 with primary muscular atrophy (PMA) or lower motor neuron predominant ALS. A cross-sectional comparison of the different ATLIS parameters between the retrospectively identified PLS and LMN ALS/PMA suggests *time to peak force* and *time to maximum rate* as potential markers for UMN involvement. To expand on the initial findings and to better identify UMN dependent parameters we are recruiting healthy controls and will compare the putative markers between healthy controls and PLS. We are also recruiting PLS participants to study those potential ATLIS parameters longitudinally and determine if they can serve as measures of disease progression in PLS and/or UMN ALS. Sensitive and objective markers of disease progression including ATLIS have the potential to detect treatment responses across different ALS variants.

381. Electrical Myotonia in Diagnosis and Monitoring of Immune-Mediated Necrotizing Myopathy

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Objective: To study electrical myotonia in diagnosis and therapeutic follow up of immune-mediated necrotizing myopathy (IMNM).

Methods: Electrical myotonia and clinical features were reviewed in IMMN vs other myopathies.

Results: Within a cohort of 119 IMNM vs 238 other myopathies, multivariate regression analysis of 20 clinical variables identified electrical myotonia and seven other clinical features highly predictive of IMNM with 96.7% area-under-curve receiver operating characteristics. Electrical myotonia occurred in 56% (67/119) of IMNM cases. Electrical myotonia favored IMNM diagnosis vs other myopathies: sporadic-inclusion-body-myositis (21%, 52/245; OR: 4.78; p<0.001); dermatomyositis (11%, 17/157; OR 10.61; p<0.001); polymyositis (13%, 39/295; OR: 8.46; p<0.001); or limb-girdle-muscular-dystrophy (14%, 28/144; OR: 5.34; p<0.001). Only in myotonic dystrophy was electrical myotonia more common (88%, 39/44). Of IMNM with myotonia 70% (37/53) had HMGCR-IgG vs 51% (25/49) antibody negative and 29% (5/17) SRP54-IgG positive. Delay in diagnosis with multiple muscle biopsies occurred in 24% having electrical myotonia (16/67, mean 8 months; range 0-194). Treatment follow up with serial EMGs showing electrical myotonia was available in 19 (median follow-up 21 months, range 2-124). Among them, electrical myotonia was reduced from 37% (60/162) of sampled muscles to 7% (8/121; p<0.001). Reduced myotonia correlated with clinical stabilization or improvement in 64% (9/14), with median creatinine kinase reduction of 1779 U/L (range 401-9238, p<0.001).

Conclusions: Discovery of electrical myotonia can facilitate a clinico-sero-pathological diagnosis of IMNM and serve as a useful biomarker in immune therapy monitoring. Scoring electrical myotonia with seven other clinical variables can assist early recognition of IMNM.

383. A Unique Presentation of Severe Dysautonomia in Guillain Barre' Syndrome (GBS)

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Introduction: GBS is an acute monophasic illness usually provoked by a preceding infection. Approximately 70% of patients present with dysautonomia, which can be severe in up to 20% of cases. Common symptoms include tachycardia, urinary retention, and hypertension alternating with hypotension, orthostatic hypotension, bradycardia, arrhythmias, ileus, and anhydrosis. Here, we report a unique presentation of GBS with severe dysautonomia.

Methods and Results: 76 y/o woman with lumbar degenerative disease s/p spinal stimulator, diabetes, hypertension, who initially presented with acute onset, diffuse pain and paresthesias in all four extremities. She reported recent sinusitis and current UTI. She was treated for UTI and discharged with the diagnosis of Diabetic Neuropathy. She presented 3 days later with a generalized tonic-clonic seizure in the setting of accelerated hypertension (243/109). CT head was unremarkable, and EEG revealed diffuse intermixed delta/theta slowing without epileptiform discharges. A week later, she presented again with acute onset R gaze preference and R sided weakness (NIHSS 22). Rapid improvement of focal deficits occurred within 20 minutes with residual encephalopathy which progressed over the subsequent day into bizarre behaviors and delusions with visual ataxia, agnosia and hallucinations. CT head showed a subtle area of decreased attenuation within the right cerebellum. Repeat imaging 9 days later demonstrated bilateral occipital hypodensities. She subsequently developed urinary retention with obstructive hydrouretur. Neurologic exam revealed weakness, areflexia , ataxia and diminished vibration sensation in the distal aspect of all four extremities. She received 5 days of high dose steroids with improvement in cognition, but persistent extremity symptoms. Blood work showed leukocytosis (16,000), Hyponatremia (122), urinary studies consistent with SIADH, elevated ESR (28), CRP (5) with normal TSH, Sjogren's Abs, cryoglobulin, B12. CSF showed albuminocytologic dissociation (protein-95 and 0 WBC). CTA demonstrated mild atherosclerotic disease. EMG demonstrated demyelinating sensorimotor polyneuropathy.

Conclusion: Overall, patient's clinical course is consistent with Guillain-Barre Syndrome. We suspect she developed severe dysautonomia which led to urinary retention, hyponatremia with SIADH-like features, accelerated hypertension leading to a Posterior Reversible Encephalopathy Syndrome (PRES), manifesting as encephalopathy/delirium, visual disturbance/hallucination, and seizures. The high-dose pulse IV steroids initially used to empirically treat presumptive encephalitis unknowingly may have treated the PRES (several case reports). CTH abnormalities isolated to the posterior circulation, consistent with changes seen in PRES. (spinal stimulator precluded MRI). EMG confirmed the diagnosis; she was treated with Intravenous immunoglobulin with gradual improvement.

384. A Unique Case of Progressive Spasticity and Profound Brain Atrophy in a Young Female

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Over 60 types of Hereditary Spastic Paraplegia (HSP) have been identified; divided between pure (mostly spasticity) and complex (spasticity with neurological features) forms that can be inherited as autosomal dominant, recessive, or more rarely, X-linked disorders. We present a unique case of progressive spasticity and cortical atrophy in a young woman, who was eventually diagnosed with Spastic Paraplegia type 11 (SPG-11). 32-year-old previously athletic female presented with more than 10-year history of cognitive decline and progressive weakness. She was in her usual state of health up until age 18 when she first presented with leg pain and difficulty running. Over the next few years, she continued to decline, unable to ambulate without a walker, eventually became wheelchair-bound. Similar symptoms started in upper extremities, though to a lesser degree, with dysarthria, dysphagia, andsome visual hallucinations. She was noted to have a mild cognitive impairment, spastic dysarthria, increased tone in both lower and upper extremities. Family history was largely negative for neuro-cognitive disorders. She was initially diagnosed with Cerebral palsy.Laboratory investigations including CBC, CMP, TSH, B12, ANA, SPEP were all within the normal range. Arylsulfatase A and long-chain fatty acids were unremarkable. Serial brain imaging over the decade revealed progressive cerebral volume loss, predominantly in the frontal lobes with normal cerebellar volumes, thinning of the corpus callosum, and minimal white matter changes. EMG findings were suggestive of a chronic lower motor neuron involvement. Due to progressive frontal lobe atrophy and lower motor neuron findings noted on the EMG, genetic testing was sent for the ALS-FTD panel, which showed 2 pathogenic mutations in theSPG11 gene, known to cause spastic paraplegia type 11. SPG 11 is the most common complex autosomal recessive disorder of the protein Spastacsin, on chromosome 15q21.1 which deals with endosomal trafficking and lysosomal biogenesis. Defects in this protein resulting inHSP cause spasticity, but also parkinsonism, maculopathy, progressive slow cognitive decline, and peripheral neuropathy. Hallmark brain MRI findings in patients with SPG11 gene mutation are thinning of the corpus callosum, so-called 'ears of the lynx deformity', as was noted inour patient and was present on her initial imaging in 2009. This suggests that imaging markers may present early in the disease course, and may prove useful in future efforts to develop treatments or early diagnostics for HSP.

385. Dual CASPR2 and LGI1 Antibody-Mediated Guillain-Barré Syndrome Associated with Severe Neuropathic Pain, Muscle Membrane Hyperexcitability, and Radiographic Evidence of Renal Cell Cancer

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Introduction: The voltage-gated potassium channel (VGKC) modulates neuronal excitability and neurotransmitter release and contributes to generation of action potentials.[1] Contactin-associated protein-like 2 (CASPR2) and leucine-rich glioma-inactivated 1 (LGI1) are membrane proteins associated with the VGKC. Autoantibodies to VGKC and these associated proteins have been implicated in numerous disorders of the central and peripheral nervous systems. They have less frequently been described in the pathogenesis of Guillain-Barré syndrome (GBS) as a paraneoplastic phenomenon.[2]

Case description: A 67-year-old previously healthy gentleman presented with ten days of progressive lumbar radicular pain, weakness, and bilateral upper and lower extremity dysesthesias. His examination revealed upper extremity fasciculations, diffuse weakness worse in the lower extremities, generalized areflexia, and stocking-glove sensory loss. CSF analysis revealed cytoalbuminologic dissociation and electrodiagnostic studies were suggestive of demyelination, axonal loss, diffuse active denervation without motor unit remodeling, reduced motor unit potential recruitment, and muscle fiber membrane hyperexcitability. MRI of the spine was notable for an incidental left renal mass concerning for malignancy. A serum paraneoplastic panel revealed CASPR2 and LGI1 antibodies. IVIg treatment resulted in improvement in pain, weakness, and areflexia. On hospital day seven, the patient developed paralytic ileus, fulminant respiratory failure, and ultimately expired.

Discussion: This patient's presentation of progressive limb weakness, areflexia, and severe neuropathic pain, coupled with cytoalbuminologic dissociation and the electrodiagnostic findings, is consistent with a diagnosis of GBS. The finding of a renal mass, although not biopsied, was highly suspicious for malignancy. CASPR2 and LGI1 antibodies are not considered typical paraneoplastic antibodies, but are posited to have mediated GBS in this patient with suspected occult malignancy. While GBS is not typically considered a paraneoplastic entity, CASPR2 antibody positivity in association with GBS has been described in patients with cancer.[2] Screening for underlying malignancy in patients presenting with otherwise unexplained GBS may therefore be fruitful.

Conclusion: This case highlights the diagnostic and prognostic value of CASPR2 and LGI1 antibodies as biomarkers of autoimmune neuropathies, and their potential role in the pathogenesis of paraneoplastic syndromes. Furthermore, this

case adds to a growing body of literature describing CASPR2 and LGI1 as biologically-plausible autoimmune targets in the pathogenesis of GBS.

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386. An Unusual Case of Acute Flaccid Paralysis Associated with West Nile Virus Involving Paraspinal and Bulbar Muscles

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Background: The most common neuromuscular manifestation of West Nile virus (WNV) infection is an acute flaccid paralysis, usually asymmetric and variably involving one to four limbs. It may associated with fever or meningoencephalitis. Bulbar palsy has been observed frequently in the course of the disease, however it has been reported very rarely as an initial presentation without any other neuromuscular symptoms. We present a case of WNV infection with bulbar symptoms as the only clinical manifestation for several weeks on initial presentation.

Results: We report a case of a 63 year old homeless male who presented initially with slowly progressive dysarthria, dysphagia, and dysphonia, followed by bilateral limbs weakness after 6 weeks. Neurological exam revealed lower bulbar muscle involvement and decreased in muscle strength at cervical paraspinal muscles and bilateral lower and upper extremities, asymmetrically (with more involvement of lower extremities), associated with absent DTRs at bilateral knees and right ankle, and patchy muscle atrophy at bilateral upper and lower extremities especially at bilateral thenar and anterior tibial muscles. Whole spine MRI showed no evidence of canal stenosis or myelopathy, and only revealed mild to moderate foraminal narrowing at C3-C4 and L5-S1 levels. Brain MRI reported no abnormality except mild chronic microvascular changes. Routine blood work up and inflammatory markers including CRP and ESR were unremarkable. Initial EMG study showed evidences of acute denervation and chronic reinnervation pattern in most studied muscles especially at paraspinal and tongue muscles most likely consistent with ALS. CSF analysis revealed elevated WBC (WBC: 154) with lymphocyte predominance and high protein but no RBC. Initial viral and bacterial meningoencephalitis panel from CSF was negative. Paraneoplastic and autoimmune encephalitis panel from CSF and serum showed no significant abnormality, but further CSF study revealed positive IgG and IgM antibody tests for West Nile virus which was consistent with recent WNV infection.

Conclusions: Lower bulbar dysfunction including dysphagia, dysphonia or respiratory failure usually follows or are concurrent with limb weakness in patient with WNV infection. Bulbar symptoms were the first manifestation of West Nile virus infection on our patient and should warrant clinical providers to be aware of this unique presentation in their differential diagnosis.

387. Hu-Dat? A Case of Paraneoplastic Sensory Neuronopathy and Cerebellitis

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Background: Paraneoplastic syndromes predominantly affecting the nervous system may present upto five years prior to unmasking a primary malignancy. We discuss a case of positive anti-Hu antibody that mimicked Miller-Fisher syndrome.

Case: A 60-year-old man presented with acute onset of difficulty walking and binocular double vision. He had no recent illness, fever or diarrhea. His examination showed severe appendicular ataxia, unsteady gait and absent deep tendon reflexes with bilateral downgoing plantar responses. He had a complete loss of vibration and proprioception with patchy loss of pin prick sensation. He had profound pseudo athetoid finger movements. Muscle strength was relatively preserved in the upper and lower limbs. A very mild right cranial nerve six palsy was noted. Cerebrospinal fluid (CSF) examination revealed 41 white blood cells, protein of 107 mg/dl and glucose of 77 mg/dl. There were 9 CSF specific oligoclonal bands and a normal CSF IgG index. Magnetic resonance imaging of the brain was normal. Miller Fisher syndrome or sensory ataxic variant of GBS was suspected and he received IVIG x 5 days. Although Anti-ganglioside antibodies like GM1, GD1a, and GD1b came back positive, GQ1b was negative. A continued decline beyond 8 weeks prompted exploration for alternate etiology and nerve conduction studies and electromyography confirmed our clinical suspicion of a sensory neuronopathy. Anti-Hu paraneoplastic antibody was positive in serum (1: 7680) and CSF (1:256). High dose Intravenous steroids followed by oral maintenance doses were initiated to treat the dorsal root ganglionopathy. Over the course, evolution of direction changing nystagmus and scanning quality of speech suggested an additional cerebellar pathology. Positron emission tomography (PET) scan showed increased metabolic activity in the right supraclavicular lymph node. Its biopsy confirmed a metastatic small cell carcinoma. A course of plasma exchange followed by periodic maintenance IVIG showed no improvement. He is committed to periodic cancer surveillance.

Conclusion: Anti-Hu paraneoplastic antibody can lead to a syndrome of acute cerebelltis as well as dorsal root ganglionopathy and warrants an aggressive search for primary malignancy. In our case, presence of serum and CSF anti-Hu antibodies, electrodiagnostic evidence of sensory neuronopathy and continued clinical progression with evolution of new deficits despite aggressive immunomodulatory treatments led to the diagnosis of a severe paraneoplastic syndrome.

388. Droopy Eyelids: Think Beyond the Conventional Paradigm!

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Background: Eyelid droop with or without ophthalmoplegia can be seen in Guillain Barre syndrome, myasthenia gravis, botulism, muscular dystrophies (oculopharyngeal, myotonic, congenital) as well as mitochondrial disorders like Chronic Progressive External Ophthalmoplegia (CPEO) and Kearns-Sayre syndrome (KSS)[1]. While CPEO presents as isolated bilateral progressive ptosis and ophthalmoplegia in the forties, KSS presents before age 20 with a severe form of CPEO with pigmentary retinopathy, multisystem involvement and is often fatal.[2] Pathogenic mutations in *POLG* gene may sometimes cause CPEO with multisystemic involvement termed CPEO plus syndrome.[3]

Case Report: 41-year-old man presents with slowly progressive bilateral eyelid droop, blurry vision, rare accounts of diplopia, mild hearing loss and muscle cramps in lower limbs and gait difficulty since his early-30s. He recalls his mother and maternal grandfather too had droopy eyes and mother had multiple organ complications. Neurological exam showed bilateral symmetric eyelid droop with normal extraocular movements but slow saccades with subjective double vision on extremes of lateral gaze. There was distal loss of sensation in the feet with a positive Romberg's sign. Ophthalmology evaluation suggested bitemporal optic atrophy but no pigmentary retinopathy. Testosterone levels were low at 143 ng/dL (normal range 241-827 ng/dl). Normal cardiopulmonary diagnostics. Magnetic resonance imaging of the brain showed mild frontal atrophy but no cerebellar atrophy. A mitochondrial disorder was suspected. Genetic testing confirmed a heterozygous pathogenic mutation in OPA1 (c.1462 G>A, p.Gly488Arg) leading to optic atrophy. Additionally, two heterozygous mutations were seen in POLG (c.752 C>T and c.1760 C>T, p.Thr251Ile and p.Pro587Leu). With the age of onset in the mid-thirties, milder multisystemic features and absence of pigmentary retinopathy, CPEO plus syndrome was more likely than KSS.

Discussion: Inheritance of CPEO can be sporadic, maternal, autosomal dominant or recessive with mutations in the mitochondrial or nuclear DNA genes (POLG, C10orf2, RRM2B, SLC25A4, POLG2, DGUOK, and SPG7).[4] POLG mutations can either cause isolated CPOE with proximal myopathy or an additional multisystemic syndrome characterized by variable degrees of axonal neuropathy, ataxia, sensorineural hearing loss, depression, parkinsonism, hypogonadism, and cataracts called CPEO plus syndrome[3], as seen in our patient. Management of CPEO and its subsets require a multifaceted approach with neurology, ophthalmology, genetics, and cardiology, with symptomatic treatment markedly improving the patient's quality of life.

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389. Neurotypical Control Testing of an 8-Channel BCI Speller

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Brain Computer Interface (BCI) technologies refer to devices that use brain activity as input signals to control assistive machines. Although these are most commonly associated with limb prosthetics, the principles of BCI can be applied to many tasks. One potential application is in patients with advanced neuromuscular disorders such as amyotrophic lateral sclerosis (ALS). These patients may have preserved cognitive function, but are unable to communicate through speech or writing due to progressive loss of voluntary motor function. Most conventional communication devices for these patients rely on eye-tracking software, in which, patients look at a specific location to select a letter or action. However, as the disease progresses, ALS patients may even lose ocular movements and can no longer use these systems. Alternative systems that rely solely on brain signal input are too unwieldly, too slow, or too expensive to be practical (reaching up to $24,000; McCrimmon et al., (2016) *IEEE Transactions on Biomedical Engineering*, *64*(10), 2313-2320). We previously suggested that an 8-channel EEG-based BCI speller program could interpret brain signals from imagined finger tapping through Mu-rhythm suppression detection, which would be run through a classifier algorithm in real-time to transcribe these signals into Morse code. Such a device could represent a low-cost and practical communication tool for those with severe disabilities. We now build upon this previous proposal by testing this device in Neurotypical controls in a randomized block design in which the system will attempt to interpret signals and discriminate between two basic letters of Morse code in real time.

390. Recurrent Malignant Thymoma in Refractory Myasthenia Gravis

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Objective: To report a case of myasthenia gravis with recurrent malignant thymoma causing resistant to medical and surgical management.

Background: Thymomas are epithelial tumors arising in the thymus that are associated with several paraneoplastic syndromes. 30% of patients with thymomas will develop paraneoplastic myasthenia gravis (MG), an autoimmune neuromuscular junction disorder classically characterized by fluctuating weakness in ocular, bulbar, limb, facial, and/or respiratory muscles.

Case Report: 36-year-old female with history of thymoma treated with debulking and partial resection presented to the emergency center 5 years after surgery with symptoms of chest pain, dysphagia, intermittent facial droop, progressive generalized muscle weakness and difficulty breathing. She was found to have a recurrent anterior mediastinal thymoma. She also had positive AChR blocking, binding, and modulating antibodies, and negative anti-MuSK antibodies. She was diagnosed with myasthenia gravis and started on pyridostigmine and prednisone. She had a repeat debulking surgery and partial resection of the mass, however when followed over 1 year her symptoms did not improve. One year later, thorax CT showed once again recurrence of the mass and patient was admitted to the hospital with dyspnea requiring intubation for airway protection. Immunotherapy

was restated with multiple rounds of Plasmapheresis and IV Immunoglobulin, however patient did not improve and remained on mechanical ventilation. Patient had a tracheostomy and was transferred to a long-term acute care facility for weaning off the ventilator.

Conclusion: Recurrent thymoma is an uncommon underlying condition associated with refractory MG, and recurrence rates are 14.8%. In refractory MG patients, recurrent thymoma should be considered even with previous surgical resection of the thymoma. Although definitive treatment for patients that present with comorbid thymoma and MG is surgical resection of the neoplasm along with immunotherapy, however, the outcome could be varied, and further study is needed for optimal management of such refractory MG patient with multiple recurrent thymoma.

391. Machine Learning Optimized Dynamic Meta-Analysis to Assess and Predict the Multifactorial Nature of Amyotrophic Lateral Sclerosis

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Homeostatic instabilities in regulatory mechanisms utilized by the superoxide dismutase 1 glycine 93 to alanine (SOD1 G93A) transgenic mouse are postulated to considerably impact Amyotrophic Lateral Sclerosis (ALS) disease progression. Currently, there is experimental evidence of regulatory dysfunctions in the SOD1 G93A mouse, but studying these multifactorial and multi-scalar dynamics in vivo is difficult. Thus, to assist in better understanding complex regulation, two separate computational models of wild-type (WT) and ALS mouse physiological regulation were developed using a combination of dynamic meta-analysis (DMA), global optimization and unsupervised machine learning. Experimental data collected from untreated WT and ALS mice was partitioned into a set for model construction and a set for model validation. The developed in silico models construct a controlled network of multifactorial and multi-scalar regulatory mechanisms encompassing apoptosis, bioenergetics, chemistry, excitotoxicity, inflammation, oxidative stress, proteomics, and mouse systemic function (e.g. rotarod performance, grip strength, body weight, etc.). 110 experimentally measured metrics which describe molecular mechanisms affecting ALS pathophysiology were grouped into 14 discrete aggregation schemes representing the aforementioned 7 pathophysiological ontologies. Control feedback gains for DMA were calculated from experimental data to predict how interacting mechanisms change as a function of time and disease progression. A genetic algorithm was used to optimize missing experimental gain values for the in silico WT and ALS models. Following model validation, principal component analysis (PCA) was used to find, interpret, and visualize systemic features in the temporal ALS regulatory dynamics. Visualized in silico dynamics illustrates that ALS does indeed have substantial oscillatory instabilities that impact multiple regulatory mechanisms, and these instabilities worsen with disease progression. In contrast, WT mice only have small oscillations during early growth, but their dynamics stabilize through adulthood. We hypothesized that re-stabilizing the dynamics of ALS pathophysiology could result in halting ALS disease progression. Thus, 100 simulations of the constructed in silico ALS model were used to identify which combinations of regulatory mechanism gains must be up- or down-regulated in order to re-stabilize the ALS dynamics to approximate WT homeostasis. Identification of these ALS regulatory gains will be used to determine and simulate specific combination treatment strategies for ALS. Future work will assess combination therapeutics in silico to determine the most promising strategies for future experimental preclinical testing.

K-598. Macrophage-derived Vascular Endothelial Growth Factor-a Is Integral To Neuromuscular Junction Reinnervation After Nerve Injury

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Purpose: Functional recovery of the end target muscle after nerve injury is linked to neuromuscular junction (NMJ) reinnervation. After nerve injury, terminal Schwann cells (tSCs) extend cytoplasmic processes between NMJs to guide axon growth and NMJ reinnervation. The mechanisms related to NMJ reinnervation are not known.

Methods: We utilized sciatic nerve cut and repair in multiple mouse models to investigate NMJ reinnervation, specifically whether vascular endothelial growth factor-A (Vegf-A) at the end target muscle is crucial to establishing reinnervation.

Results: Both macrophage number and Vegf-A expression increased in end target muscles after sciatic nerve injury and repair. By the third day post-injury, Vegf-A expression increased significantly (p=0.0157) compared to uninjured muscles, and peaked at day 14 ($p<0.001$). In mice with impaired macrophage recruitment (*$Ccr2^{-/-}$ mice*), NMJ reinnervation was significantly decreased compared to controls at 14 days ($Ccr2^{-/-}$= 31%, W = 58.1%, p=0.0016) and 21 days after injury ($Ccr2^{-/-}$=74%, WT=93.7%, $p<0.001$) after sciatic nerve cut and repair. Similarly, compound muscle action potential (CMAP) values were significantly lower (p =0.035) for $Ccr2^{-/-}$ mice (9.17 $\pm$ 1.3 mV) compared to WT mice (10.91 $\pm$ 1.1 mV). Using a Vegf-Receptor 2 inhibitor (Cabozantinib) via oral gavage in wild type mice resulted in reduced tSC cytoplasmic process extension (CBZ 11% vs saline controls 22%, $p<0.05$) and decreased NMJ reinnervation (CBZ 18.7%, Saline 34.1%, p = 0.048) at 14 days after injury. Mice with Vegf-A conditionally knocked out in macrophages ($Vegf\text{-}A^{fl/fl}$; $LysM^{Cre}$ mice) demonstrated fewer tSC processes compared to controls at all time points up to 21 days, significantly ($p<0.001$) less NMJ reinnervation at 21 days, and significantly (p=0.029) worse functional muscle recovery (only 56% of controls) at 42 days.

Conclusions: Together these results show macrophage-derived Vegf is integral for NMJ reinnervation and functional muscle recovery after nerve injury.

512. In-Vivo Two-Photon Imaging Reveals Brain Capillary Plugging during Neurotoxicity in a Mouse Model of Chimeric Antigen Receptor (CAR) T Therapy

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Background: Cancer immunotherapy with CAR-T cells causes neurotoxicity in about 40% of patients, and fatal cerebral edema in 1-2%. It remains poorly understood how the systemic cytokine storm during CAR-T cell proliferation leads to brain dysfunction. We have previously shown that mice treated with murine CD19-directed CAR-T cells develop systemic elevations of IL-6 and other inflammatory cytokines, behavioral abnormalities, cerebral microhemorrhages, and claudin-5 redistribution at brain endothelial tight junctions. Based on these findings, we hypothesized that the compromised neurovascular unit might alter brain capillary blood flow during neurotoxicity.

Methods: To test this hypothesis, we performed in-vivo two-photon imaging through a thinned-skull window in wild-type Balb/c mice treated with 10 million murine CD19-directed CAR-T cells, which bind normal B cells and proliferate without a cancer target. We used i.v. fluorescent dextran to label the blood plasma, and i.v. Rhodamine 6G to label leukocytes and platelets. In each imaging session, ≥3 $100\mu m^3$ blocks of primary sensory cortex were acquired under light isoflurane anesthesia. Presence or absence of blood flow within each capillary segment was determined by movement of red blood cells, which do not take up fluorescent tracer and appear as unlabeled shadows. Each animal was screened daily by a 20-item neurophenotyping exam to correlate imaging findings with behavioral changes.

Results: We found a striking and unexpected phenotype in CAR-T treated mice: 14.8% ± 0.3% of brain capillaries were plugged on day 4 after CAR-T injection (n=1; 209 capillary segments counted). This coincided with the development of abnormal neurophenotype scores. We found that the majority of capillary stalls was caused by Rhodamine-6G labeled plugs, which represent either adherent leukocytes, or platelet-rich microthrombi. The capillary plugging improved on day 6 (5.7%±2.4% of capillaries plugged; 234 segments), along with resolution of the behavioral phenotype. Capillary blood flow was normal in control mice (0.4% ± 0.4% obstructed) that received the same preconditioning chemotherapy but no CAR-T cells (n=1; 230 segments).

Interpretation: Our preliminary in-vivo two-photon studies during acute CAR-T cell neurotoxicity reveal reversible mechanical obstruction of brain capillaries as a possible mechanism of brain dysfunction. Such impairment of microvascular flow could explain cognitive changes seen in CAR-T patients. Thus, we will next determine the identity of the capillary plugs, and test whether altering their adhesion to the endothelium can mitigate CAR-T neurotoxicity.

513. Identification of Small Molecules, Proteins, and Nanoparticles That Bypass the Blood Brain Barrier Upon Intranasal Delivery

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Diagnosis and treatment of neurologic diseases remains a formidable challenge. This is in part due to the blood brain barrier (BBB), which isolates the serum from the brain parenchyma, effectively blocking passage of diagnostic and therapeutic agents from blood to brain. Intranasal delivery is a promising, albeit underexplored, method for delivering such agents to the brain. We have synthesized and screened numerous fluorescent molecules to identify those that accumulate in the mouse brain following intranasal delivery. Specifically, cypate and cypate derivatives (LS301, LS1084, and LS1085) persist in the nasal cavity and are transported to the olfactory bulb within 8-24 hours, as demonstrated by fluorescence imaging. Hydrophobicity of the molecules positively correlates with nasal cavity retention time and brain accumulation occurring over the span of weeks. Importantly, by later time points these molecules are detected not only in the olfactory bulb, but also within multiple other brain regions. We also investigated fluorescent-tagged proteins to demonstrate that wheat germ agglutinin (WGA) is retained in the nasal cavity and accumulates in the mouse brain, whereas albumin and transferrin are rapidly cleared from the nasal cavity and fail to reach the brain. Finally, we adsorbed cypate and WGA to gold nanoparticles (5nm) to effectively increase the nanoparticle retention in the nasal cavity and ultimate brain delivery. Ongoing research is aimed at modifying the hydrophobicity of known therapeutic agents for intranasal delivery and optimizing nanoparticle delivery methods to create novel theranostics for neurodegenerative and neuro-oncologic diseases.

514. Bi-Specific Natural Killer Cell Engager (BiKE): A Novel Therapy for Glioblastoma

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Glioblastoma (GBM) is a common and aggressive primary adult brain tumor. Even with the standard treatment of surgical resection, chemotherapy, and radiation, patients, on average, survive 14.6 months. Therefore, the development of an effective treatment is imperative. Recent immunotherapies hold great promise in the treatment of GBM. Bi-specific natural killer cell engagers (BiKEs), which directly link and engage natural killer (NK) cells in killing cancer cells, have been successfully used in blood-borne and several solid cancers. There has been no application of BiKE therapy in GBM. There is sufficient evidence, however, that suggest the treatment may prove beneficial in GBM. Within the GBM

environment, NK cell counts are normally low, and the NK cells that are present tend to be anergic. However, when stimulated, NK cells can effectively target tumor stem-like cells, which are responsible for the high rate of GBM reoccurrence. Since the BiKEs can enhance NK cell activity and induce proliferation, the therapy appears promising for GBM. In this study, we discuss the design of a BiKE molecule for implementation in both *in-vitro* and *in-vivo* models of GBM. A single-domain antibody (sdAb) against human CD16 was elected due to its small size and high potency in activating NK cells. We incorporated an interleukin-15 (IL-15) linker as IL-15 is a well-known enhancer of NK cell activity, induces NK cell proliferation, and does not stimulate immunosuppressive regulatory T cells. Finally, we utilized a single-chain variable fragment (scFv) against human interleukin-13 receptor α2 (IL13Rα2) generated and validated in our laboratory. IL13Rα2 binds with high affinity (K_D =1.39 x 10^{-9} M) and has been successfully implemented as a solitary treatment using either an IL-13Rα2-expressing chimeric antigen receptor (CAR) T-cell and as a bi-specific T-cell engager in pre-clinical models of GBM. The final BiKE cDNA will be synthesized and sub-cloned in lentiviral vector, pLVX-IRES-ezGreen1. Stable cells secreting recombinant BiKE will be generated via lentiviral transduction of 293T cells. Protein will be purified by affinity chromatography and used in all functional studies. The resulting molecule, termed sdCD16-IL15-scFvIL13Rα2, consisted of a single-domain antibody (sdAb) anti-CD16, an IL-15 linker, and a single-chain variable fragment (scFv) anti-IL13Rα2. Initial results from the implementation of BiKE both in an *in-vitro* and a murine model of GBM will be discussed.

515. Transposable Elements Offer Neoantigen Promise for Immunotherapy in Glioblastoma

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Among the CNS neoplasms, glioblastoma (GBM) is most common and most lethal. Profiling the GBM histologic, genetic and epigenetic landscapes enables clinical stratification of distinct patient populations with prognostic and therapeutic implications. Despite accounting for nearly half the genome content, transposable elements (TEs) have been underexplored in cancer genomic studies owing to their constitutive epigenetic repression in somatic cells. However, clinical application of DNA methyltransferase (DNMTi) and histone deacetylase inhibitors (HDACi) have shown success in reshaping the GBM epigenome. Previously, globally-mapped DNMTi- and HDACi-induced transcriptomic and epigenomic changes demonstrated that most epigenetic therapy-induced transcriptional start sites reside in TEs. Here, we show that decitabine (DNMTi) and panobinostat (HDACi) work both alone and synergistically to increase TE-expression by reversing epigenetic repression in glioblastoma stem cells (GSCs). When translated, these TE-derived transcripts are expressed on surface HLA-I, potentially enabling immunotherapy targeting of these tumor-specific antigens. Three patient-derived GSC lines, quiescent and replicating fibroblast and normal human astrocyte controls were treated with 1uM decitabine and 100nM panobinostat. Epigenomic and transcriptomic profiling utilized whole-genome bisulfite sequencing, ATAC-seq, RNA-seq and CAGE-seq. A stringent pipeline was constructed to select highly-specific TE-derived transcripts using CAGE-seq and RNA-seq, followed by in silico translation. NetMHCpan-derived HLA-binding affinity predictions of TE-derived peptide candidates were obtained with a 500nM filter to enrich for high-affinity binding antigens. Finally, HLA-I peptidome immunoprecipitation, followed by liquid chromatography tandem mass-spectrometry (LC-MS/MS) was used to validate TE-derived peptides. Computational assessment of open reading frames originating from GSC-specific TE cryptic promoter activation events revealed 36 novel transcripts. Following decitabine treatment, little change in global DNA methylation was observed in quiescent cell lines. In silico translation of TE-derived transcripts followed by NetMHCpan HLA-peptide profiling predicted an average of 20 TE-derived peptides expressed on surface HLAs with high binding affinity. Remarkably, since many TE-derived candidates are shared, the possibility of a pan-GSC TE-antigen vaccine warrants further exploration. On average, mass spectrometry-based immunopeptidomics validated 4 unique TE-derived peptide antigens. Beyond corroborating previously observed TE-promoter activation by DNMTi and HDACi, we demonstrate proteomic changes in epigenetic therapy-treated GSCs. The high specificity of LC-MS/MS, coupled with the stringent filters employed in the computational pipeline suggest a substantial degree of confidence in the display of TE-derived peptides in cell-surface HLA-I molecules. We present HLA-bound, TE-derived tumor-specific antigens as a widespread post-epigenetic therapy phenomenon with potential therapeutic value in immunotherapy regimens.

516. Streptococcus Intermedius Brain Abscess Mimicking Necrotic Tumor: Case Report

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Objective: To report two cases of brain abscess caused by *Streptococcus Intermedius* that were difficult to distinguish from cystic or necrotic tumors based on clinical and imaging findings.

Background: Brain abscess and brain tumors have similar clinical presentations. Brain abscess is a challenging clinical problem associated with high case fatality rates. Poor outcomes are associated with delayed initiation of antimicrobial therapy. Distinguishing brain abscess versus cystic or necrotic tumors is difficult based on routine computed tomography (CT) or magnetic resonance imaging (MRI) findings. Diffusion weighted imaging (DWI) is a useful diagnostic modality to differentiate abscess and metastasis but there is still overlap.

Case presentation: A 55-year old female with history of stage IV intranasal mucosal melanoma status post resection and postoperative radiation presented with headaches and vision changes. Her MRI of brain showed a ring

enhancing lesion with restricted diffusion and hemosiderin deposition suggesting hemorrhagic and possible necrotic metastasis. ENT evaluation showed ulcerative lesion of the upper palate likely related to radiation. Further evaluation of MRI showed extension of lesion to the floor of her right middle cranial fossa with a defect extending to the postoperative right maxillary bed. She underwent a craniotomy, and pathology later showed to be abscess due to *Streptococcus intermedius*. Second case is a 56-year old female with no known cancer history who presented with severe headaches, fatigue, and hemianopsia. She was afebrile and presented with leukocytosis, questionably secondary to her steroid treatment versus abscess. Her MRI showed large cystic enhancing mass of the right parietal-occipital lobe consistent with neoplastic etiology, with significant edema and mass effect. She underwent decompressive craniotomy and drainage, with pathologic findings of an intracranial abscess. The culture showed *Streptococcus arginosis* and *Streptococcus intermedius*.

Conclusion: Brain abscess is difficult to distinguish from cystic tumors due to overlap in presentation and imaging findings. These indistinguishable features can cause delay in antimicrobial therapy and subsequently lead to poor prognosis. DWI is a useful modality for distinguishing abscess and tumors but may leave some uncertainty in complex cases. Neurosurgical stereotactic techniques are essential for pathological diagnosis and decompressive management of brain abscess.

517. Whole-Brain Resting-State Mapping to Measure the Effect of Gliomas on Brain Function

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Gliomas are the most common primary tumours in adult brain. Gross total resection is associated with better outcome and prolonged survival (Kreth, AnnalsOnc2013), however, the benefits of a larger resection need to be balanced against the risk of cognitive deficits post-surgery with a reduction of quality of life (Ghinda, NeuroscienceBiobehavRev2018). Current strategies employ intra-operative stimulation or specific task/rest state functional mapping to delineate eloquent areas to be preserved during surgery. However, the influence of gliomas on distant regions whose damage can also lead to cognitive deficits is largely unexplored. Here we propose a whole-brain mapping approach based on resting-state fMRI and analysis of resting-state networks (RSNs) for a safer planning of surgery.

Methods: We studied 28 patients with newly diagnosed high- and low-grade gliomas (13F/15M; age 59.6±15.8y). Resting-state fMRI, T1w with/without contrast, T2w and FLAIR images were acquired on a 3T Siemens Biograph mMR scanner. Tumour core and edema were manually segmented by an expert neuroradiologist. Functional images were analyzed with group-information guided Independent Component Analysis performed on the publicly available MPI-Leipzig Mind-Brain-Body dataset (Mendes, SciData2019). This approach allows to identify at the level of single subjects the alteration of specific RSNs, measured as the cosine similarity value between the spatial map of each patient's RSN as compared to a group of healthy controls. We also defined the overlap between altered RSN maps and the tumour extent, including or not the region of edema.

Results: The tumour location was predominantly frontal and temporal. Several RSNs components were significantly and variably altered (range RSN components affected=0-23; mean=5.5). Most of these components were remote from the tumour region. In fact, the % spatial overlap between tumour and altered RSN components was small (3.3±3.6 % in the tumour core; 4.3±4.0 % tumour and edema). Most components localized to cingulo-opercular, frontoparietal, and visual networks. Correspondingly, most cognitive deficits were in executive function, memory, and attention.

Conclusions: Gliomas have an important functional impact on remote regions and networks. We suspect that this functional effect significantly contributes to cognitive deficits and quality of life. A whole-brain functional mapping approach entirely performed at rest could provide helpful information for tumour surgery planning and evaluation of the effect of chemo- and radio-therapy.

518. Exploring Patients' Subjective Experiences during Awake Craniotomies: Clinical Practices to Alleviate Patient Discomfort and Promote Resilience

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Background: Intraoperative functional mapping during awake craniotomies is a well-established technique to maximize lesion resection while optimizing post-operative function. While the safety and efficacy of awake craniotomies have been widely established, the literature is limited in its review of patients' subjective experiences. **Purpose:** Using a mixed-methods research design, this study explored and described the subjective experiences of a consecutive series of patients undergoing awake craniotomies for tissue resection due to medically refractory focal epilepsy (n = 1) or malignant primary brain tumors (n=14).

Methods: Individual, semi-structured interviews (n=15) were conducted at the 2-week postoperative appointment with ambulatory adult patients who underwent an awake craniotomy. Postoperative interviews were audio-recorded, and transcribed. Data was then analyzed in April and May of 2020 using a conventional content analysis to systematically examine material and obtain a condensed description of content. Triangulation was employed to increase the validity of

the results. Preoperative levels of generalized anxiety, anxiety specific to the procedure, depression, and trauma symptoms, and postoperative levels of generalized anxiety and depression were collected using validated and widely used self-report measures. Postoperative rating scales measured patient reported intra-operative pain, overall distress, anxiety, distress due to noise, perception of agency, level of preparedness, and overall satisfaction with the procedure and anesthesia management. Pearson's correlations coefficient examined relationship between variables.

Results: Six overarching themes emerged: 1) recollection of intraoperative sensations, including pain; 2) most stressful aspects of the procedure; 3) clinical practices and processes that successfully alleviated stress and discomfort; 4) clinical practices that promoted patients' perceptions of agency and resilience; 5) behavioral and mental-emotional postoperative changes; and 6) suggested recommendations for medical teams. Overall distress was positively associated with intraoperative noise and anxiety and inversely associated with perceptions of anesthetic management.

Conclusion: Results reflected positively on the patients' awake surgery experience; however, there were some areas that necessitate improvement. Importantly, patients' perspectives provided insight into clinical practices and processes during the procedure that may alleviate stress and discomfort and promote patients' perceptions of agency and resilience, such as cultivating an authentic relationship(s) with the patient in the operating room, responding quickly to patient requests, and providing structured tasks and timelines. Understanding patients' experiences may shed light on areas of needed quality improvement and can lead to better delivery of care and improved health outcomes.

519. Acute-Onset Throbbing Headache, a Rare Manifestation of Sphenoid Wing Meningioma: A Case Report

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Introduction: Meningiomas are common tumors that account for 13-20% of all the intracranial tumors. Sphenoid ridge meningiomas constitute approximately 20% of supratentorial meningiomas, of which less than 50% arise from the medial sphenoidal ridge. Usually, they present with a classical clinical triad consisting of proptosis (86%), visual impairment (78%), and ocular paresis (20%). Chronic headaches are also a common manifestation but sudden-onset headaches with severe intensity and throbbing quality, are very rare.

Methods: We report here a case of acute-onset severe headache attributable to a sphenoid wing meningioma, a very rare presentation of the tumor.

Results: This case concerns a 46-year-old woman who presented to our emergency department with a sudden onset of headache which was severe in intensity. Computed tomography, cerebral angiogram and magnetic resonance imaging showed a right sphenoid wing meningioma with right frontal and temporal lobe compression and midline shift, which was pathologically confirmed as an atypical meningioma WHO type II. The patient underwent timely surgical tumor resection and had a good prognosis.

Conclusion: This case illustrates and reinforces the importance of excluding underlying pathology in patients presenting with an acute-onset severe headache. Neurologists and neurosurgeons need to be aware of this rare presentation amongst patients with sphenoid wing meningioma to avoid a delay in diagnosis and appropriate management.

520. An Atypical Presentation of Lymphomatosis Cerebri

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Lymphomatosis Cerebri (LC) is a rare infiltrative variant of primary CNS lymphoma (PCNSL) that appears diffuse on imaging without evidence of a discrete mass. LC is a diagnostic challenge given its rarity and atypical presentation on imaging in comparison to other CNS lymphomas which typically appear mass-like. The purpose of this presentation is to help increase diagnostic accuracy and awareness of LC. A 71-year-old female with history of depression and anxiety presented for evaluation of rapidly progressive ambulatory dysfunction. Initial head CT demonstrated only advanced chronic white matter changes. Patient was subsequently admitted to the psychiatric unit a month later for increased anxiety and behavioral disturbances. She developed apraxia and aphasia prompting a neurology consultation. Brain MRI demonstrated diffusely increased FLAIR signal throughout the pons, midbrain, internal capsule, corpus callosum, corona radiata, and centrum semiovale with extension into the subcortical white matter. There was a punctate ill-defined area of enhancement within the affected area of the right frontal lobe. No mass effect or midline shift was demonstrated. Affected areas in the subcortical white matter were fairly symmetric in appearance and were suggestive of leukoencephalopathy or demyelinating disease. Cerebrospinal fluid (CSF) analysis demonstrated 40 wbc/μl, otherwise infectious, inflammatory, and autoimmune serological CSF studies were unremarkable, including cytology. Eventual brain biopsy confirmed Diffuse Large B-cell Lymphoma or LC. Patient developed a rapidly deteriorating dementia within months of the diagnosis and expired from the disease. PCNSL represents only 2.5 % of all brain tumors. Lymphomatosis cerebri (LC) is a rare subtype of PCNSL that exhibits a diagnostic challenge given its subacute clinical presentation and diverse differential on imaging which typically includes infection, leukoencephalopathy and autoimmune diseases. There's no clear neuroradiological criteria identified, but some small case series demonstrate diffuse and asymmetric abnormal T2-hyperintensity in deep and subcortical white matter along with grey matter involvement. Our case is unique in that it represents fairly symmetric involvement of the subcortical white matter and deep grey matter structures. Her initial clinical presentation was also unique given that

she presented with gait dysfunction as opposed to cognitive deficits & dementia which are more characteristic of LC. This case hopes to elicit awareness of LC's atypical variants on imaging and clinical presentation to provide accurate diagnosis.

521. Relapsed Diffuse Large B-cell Lymphoma (DLBCL) with Leptomeningeal Carcinomatosis Treated with Intrathecal Chemotherapy

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Diffuse large B-cell lymphoma (DLBCL), a subtype on Non-Hodgkin lymphoma (NHL), infrequently relapses with secondary CNS involvement (5%). Once leptomeningeal metastasis has been identified, prognosis is poor and treatment strategies are palliative based. Reported interventions have included systemic/intrathecal chemotherapy and/or radiotherapy. We report a unique case with prominent MRI findings. 58 year-old-man was hospitalized for acute encephalopathy associated with worsening lower extremity weakness. He had a notable PMH of diffuse large B-cell lymphoma (DLBCL) in remission s/p treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and herpes zoster (VZV) infection of the right chest s/p treatment with famiciclovir. On examination, he was disoriented, decreased attention/concentration span, multiple cranial neuropathies (bilateral CN III, left CN VI, and left CN VII), hypotonia, hyporeflexia, and muscle weakness rated 2-3 out of 5. He underwent extensive worked up including magnetic resonance imaging (MRI) of the entire neuroaxis and lumbar puncture with cerebrospinal fluid (CSF) analysis. Imaging revealed enhancement of multiple cranial nerves, extensive leptomemingeal enhancement of the spinal cord, and marked thickening of cauda equina nerve roots. CSF morphology and immunotyping was consistent with CNS involvement of large B-cell lymphoma. Specifically, he had significantly elevated CSF WBC with large atypical cells, convoluted nuclear contours, prominent nucleoli, and agranular blue cytoplasm on pathology review. Additionally, flow cytometry demonstrated monoclonal lambda-restricted CD20+ B-cell population. He was treated with intravenous dexamethasone and intrathecal methotrexate, cytarabine, rituximab, and hydrocortisone. While his mental status was seen to greatly improve, he remained with significant weakness and was eventually discharged to inpatient rehabilitation. While rare, relapsed DLBCL with leptomeningeal carcinomatosis may present as multiple neurological complaints. Despite poor prognosis, intrathecal chemotherapy can ameliorate symptom burden. Neuroaxis imaging should be obtained to better characterize extent of disease progression, and CSF analysis should be performed to help guide therapy.

522. First Dose Pembrolizumab-Induced Toxicity in Young Patient Treated for Invasive Thymoma: An Overlap Syndrome of Myasthenia Gravis and Myositis

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Background: Immune checkpoint inhibitors (ICIs) are revolutionary agents that enhance T-cell mediated recognition and destruction of malignant cells and reactivate the immune system for a long-lasting antitumor response. Immune-related adverse events occur due to an autoimmune reaction affecting multiple organs. Neuromuscular complications have been estimated from 2 weeks to 20 weeks of initiation of ICIs. Rapid progression, as well as higher morbidity and mortality are expected with these syndromes compared to idiopathic cases. Most common manifestations include myasthenia gravis, followed by myositis, and Guillain-Barre syndrome. The following case represents a seropositive myasthenia gravis with myositis as an overlap syndrome in a patient after the 1st cycle of ICI therapy.

Case Presentation: A 34-year-old female with history of invasive thymoma who underwent a radical thymectomy, radiation and chemotherapy, received her 1st infusion of pembrolizumab immunotherapy for suspected tumor recurrence. Five days later, she experienced progressive fatigue, severe eyelid swelling and maculopapular skin rash on the arms and trunk. Over the next 2 weeks, she developed worsening bilateral ptosis, ophthalmoplegia, generalized muscle aches and dyspnea on exertion. She denied history of pre-existing autoimmune or neurological disorders; however, was never tested prior to initiation of immunotherapy. Her exam was remarkable for severe bilateral ptosis and near complete ophthalmoplegia, dry eyes and mouth, weakness on neck extension, significant orthopnea and myalgias in proximal lower extremities. Labs revealed high titers of acetylcholine receptor binding antibodies at 1.9 nmol per liter. Elevated levels of creatinine kinase, troponin, and liver enzymes are suggestive of myositis. Other autoimmune and paraneoplastic panels were negative. Initial treatment with Dexamethasone 10mg every 8 hours had minimal benefit. Subsequently, patient received empiric intravenous methylprednisolone 1 gram per day for 3 days and Pyridostigmine 30-60 mg daily with improvement in ptosis, extraocular movements and breathing. She was discharged from the hospital on Prednisone taper and advised to follow up with neurology.

Discussion: Our case is unique in a way that our patient developed overlap syndrome after only 1 dose of Pembrolizumab. Neuromuscular adverse events can lead to life-threatening complications and must be recognized and managed early. Additionally, it is vital to emphasize thorough screening of patients prior to initiation of immunotherapy. Pre-existing autoimmune conditions may be considered a relative contraindication for ICI therapy due to higher risk of relapse or more rapid clinical deterioration.

523. Pre-Infusion Neurofilament Light Chain (NfL) Levels Predict the Development of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

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Background: Chimeric antigen receptor-modified (CAR) T cell therapy has revolutionized the treatment of refractory B cell malignancies (Hunter, *J Natl Cancer Inst*, 2019). Neurological side effects are common, with symptoms observed in approximately half of all patients (Rubin, *Brain*, 2019). Termed immune effector cell-associated neurotoxicity syndrome (ICANS), symptoms range from mild encephalopathy to seizures, and diffuse cerebral edema. No predictive biomarkers exist to identify individuals at risk for developing ICANS. Serum neurofilament light chain (NfL), a well-established marker of neural injury, and glial fibrillary acidic protein (GFAP), a biomarker of astrogliosis are known to dynamically change in neuro-inflammatory disorders (e.g. multiple sclerosis). We hypothesized individuals undergoing CAR T cell therapy who ultimately developed ICANS would have early and sustained elevations in serum NfL and GFAP.

Methods: We performed a retrospective analysis of serum samples from 11 individuals treated with tisagenlecleucel or axicabtagene ciloleucel (mean age 61.3, 18% female, 27% ICANS, all with peak severity score 3). Most individuals had a longitudinal sampling at baseline, pre-infusion, post-transfusion day (PTD) 1, PTD 3, PTD 7, PTD 14, and PTD 30. Serum NfL and GFAP were assayed using a Simoa HD-1/HD-X kit (Quanterix^{TM}). Group comparisons for serum NfL and GFAP were compared between individuals who developed ICANS and those who did not using direct unpaired t-tests, followed by a receiver operating characteristic (ROC) curve for classification.

Results: Individuals who developed ICANS had early and sustained elevations in serum NfL levels at baseline (p **= 0.0075**), pre-infusion (p **= 0.0172**), and PTD 3 (p **= 0.0026**) and PTD 30 (p **= 0.0066**). All group comparisons survived multiple comparison testing using false-discovery rate (FDR). No significant group difference in serum GFAP levels were observed at any timepoint between the groups. ROC curve classification by logistic regression of serum NfL revealed an area under the curve (AUC) of **1.0** with a cut-off of 44 pg/mL. No correlation was observed between NfL levels and age, sex, or history of central nervous system involvement of the underlying malignancy.

Conclusion: Serum NfL levels and not GFAP are a robust early marker for the development of ICANS, even before infusion. NfL levels remained elevated even after resolution of the acute phase of the syndrome. Our findings suggest the risk of developing ICANS reflects pre-transfusion host-factors, permitting the screening well in advance of drug administration.

524. Primary Lumbar Spinal Epidural B Lymphoblastic Lymphoma Initially Misdiagnosed as Chronic Back Pain

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Introduction: Primary spinal epidural Non- Hodgkin's lymphoma (PSENHL) is one of the rarest central nervous system tumors. The majority of PSENHL are diffuse large B-cell lymphomas, usually seen in 40-50 year age. It affects mid-thoracic spine (69%), lumbar spine (27%), and cervical spine (4%). Pathogenesis of PSENHL is unclear, the role of a chronic inflammatory process, chronic infection, autoimmune disease is assumed.[1]

Case: A 51-year-old male presented with worsening back pain radiating to right lower quadrant of the abdomen for 4 months. The pain was dull, 7/10 in intensity, worsening with movement, minimal relief with analgesics. He denied fever, weakness, weight loss, bowel, and bladder dysfunction. He had a traumatic injury of back 16 years ago leading to chronic back pain, which was treated with intraarticular steroid injection. Lately, his back pain continued despite the frequent injections. Magnetic resonance imaging (MRI) spine revealed enhancement of T10 vertebral body with 0.5 cm focus of abnormal signal suggestive of an abscess vs spondylitis vs neoplastic process. Computed Tomography guided aspiration biopsy of the mass was negative for infection and malignant cells. He underwent a T11 laminectomy with total resection of the mass. Histopathological examination showed diffuse large B-cell lymphoma, germinal center B-cell type. It was positive for LCA, CD10, CD20, CD 79a, and BCL 6 with a Ki-67 proliferation index of 80%. The final diagnosis of primary spinal epidural diffuse large B-cell lymphoma was made. Postoperatively his back pain improved and was treated with prednisone. Positron emission tomography (PET) scan, bone marrow biopsy was negative. Currently, he is undergoing evaluation by the oncology team.

Discussion: PSENHL may initially present with chronic back pain or radicular pain progressing to spinal cord compression, later progressing to neurologic deficits like paresis, ataxia, sensory disturbance with bowel and bladder incontinence. Pathological compression fractures, infectious lesions, or carcinomatous deposits can mimic similar presentations and it is difficult to diagnose. Emergency decompressive surgery, with or without resection, in the acute phase followed by radiotherapy and chemotherapy can be the mainstay of treatment.

Conclusion: Therefore, physicians should be cautious and do a further workup to rule out this rare condition, as early intervention may prevent further worsening of symptoms, improves functionality and quality of life

Reference: 1. Cho H J, A rare case of malignant lymphoma occurred at spinal epidural space: a case report. Korean J Spine. 2015;12(03):177-180t

Neuro-Ophthalmology

135. Neurosarcoidosis Related Vision Loss Mimicking Idiopathic Intracranial Hypertension

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Objective: To present a case of recurrent vision loss in a patient with presumed idiopathic intracranial hypertension (IIH), who was ultimately found to have optic neuritis as the primary manifestation of sarcoidosis.

Background: Sarcoidosis is an inflammatory condition characterized by non-caseating granulomas that can affect

multiple organs but most commonly involves the lungs. Ocular involvement occurs in up to 25% of patients and is the primary presenting manifestation in 5% of the cases. Uveitis is seen most frequently, but patients may also present with optic neuritis.

Design/Methods: A 56-year-old woman developed left eye vision loss, papilledema, and increased CSF opening pressure three years ago. At that time, extensive diagnostic testing, including MRI of the brain and CSF inflammatory markers, was unremarkable. Acetazolamide was prescribed to treat presumed IIH. She recently presented with two weeks of worsening visual acuity in the right eye. Fundoscopic exam showed pallid optic discs with edema. MRI evidenced a mildly engorged right optic nerve sheath with bulging of the right optic disc and mild chronic left optic neuritis with atrophy and patchy left optic nerve sheath enhancement. CT chest revealed mediastinal and bilateral hilar lymphadenopathies. Lymph node biopsy reported non-caseating granulomas without acid-fast bacilli or fungal organisms. Serum and CSF angiotensin converting enzyme levels were significantly elevated. Opening pressure remained elevated. She was diagnosed with neurosarcoidosis-related optic neuritis and was treated with high dose prednisone with remarkable improvement in her vision.

Conclusions: This is an unusual case of neurosarcoidosis initially mimicking IIH with papilledema and elevated opening pressure. However, chronic optic neuritis and nerve sheath enhancement led to further diagnostic testing which was consistent with sarcoidosis. Neurosarcoidosis should be considered in the differential diagnosis of IIH, especially in cases with unusual manifestations.

136. Retinal Amyloid Count as a Predictor of Hippocampal Volume and Cognitive Score: A Cohort Study

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Retina, the only CNS tissue not shielded by bone, is progressively expanding into an accepted diagnostic tool and potential therapeutic window for different cerebral conditions. With the accumulation of intraretinal and cerebral amyloid-beta (Aβ) plaque in Alzheimer's disease (AD)-related cognitive disorders, retinal amyloid imaging uniquely advances the field by offering earlier and more accessible detection. Given the very recent reporting of retinal amyloid imaging findings, however, the topographic and quantitative assessment of retinal amyloid burden in patients with cognitive impairment remains poorly understood. Here, we investigated 34 patients with cognitive decline using curcumin-labeled retinal autofluorescence imaging. We quantified retinal amyloid area and count in the supero-temporal quadrant and its divisions in addition to their correlation with demographic and brain volumetric parameters. The total retinal amyloid count was significantly increased in patients with higher Clinical Dementia Rating (CDR) (p=0.02). Notably, total retinal amyloid count significantly correlated with hippocampal volume (HV) (r=0.39, p=0.04) and CDR (r=0.38, p=0.02). Upon subregion analysis, only the proximal mid-periphery (PMP) demonstrated significantly greater amyloid in subjects with worse dementia (p=0.03). Similarly, PMP amyloid count correlated with HV (r=0.41, p=0.03). Overall, our cohort study indicates that retinal amyloid count may predict HV and cognitive scores. Future larger studies are warranted to validate these findings and to determine the diagnostic specificity of retinal amyloid imaging in various cerebral illnesses.

137. The Platysma in Hemifacial Spasm (HFS)

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Objective: Can the platysma aid in the diagnosis of HFS?

Background: Thought to be a neurovascular compression syndrome HFS is commonly characterized "by unilateral twitching of one side of the face," however other CN VII innervated muscles such as the platysma which abets frowning or the stapedius can be involved. Unique among muscles of facial expression, the platysma (and frontalis) are vestigial remnants of the panniculus carnosus which many animals, especially horses, use for "twitching their skin." (Darwin, *The Descent of Man* 1875)

Methods: The charts (from 11/2017 to 5/2020) of 26 consecutive (22 women and 4 men, mean age: 66.8 years) patients receiving botulinum toxin type A injections for HFS (17 out of 18) or blepharospasm/Meige (8) were reviewed. Platysma bulk and segmentation during contraction/relaxation were repeatedly examined and digitally photographed.

Results: HFS was right-sided (10 patients) or left-sided (8 patients.) and blepharospasm was asymmetrical in 2/8 patients. 14 HFS (and 2 asymmetrical blepharospasm) patients had ipsilateral platysma hypertrophy. 4 HFS and 6 blepharospasm patients had bilaterally symmetrical platysma bulk. HFS patients had significantly greater (Fisher's Exact Test p<.05) frequency of unilateral platysma hypertrophy than blepharospasm patients.

Conclusion: Ipsilateral platysma hypertrophy is presumably associated with increased activity of the cervical branch of CN VII and (despite chemodenervation) is a sign of HFS and sometimes asymmetrical blepharospasm.

138. Interim Results of the MBCT-Vision Study Show Improvement of Visual Snow Syndrome (VSS) in the First Treatment Trial for VSS

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Thomas' NHS Foundation Trust, London, United Kingdom, [2]South London and Maudsley NHS Foundation Trust, London, United Kingdom.

Background: Visual Snow Syndrome (VSS) is a condition of persistent flickering dots in the visual field. Functional imaging shows neuronal dysregulation. To date, no treatment trials in VSS have been published. Functional imaging in persistent photophobia despite treatment of identifiable ocular causes, also shows neuronal dysregulation. Mindfulness-Based Cognitive Therapy (MBCT) is an evidence-based clinical intervention to develop skills of mindfulness and cognitive behavioural therapy (CBT) strategies, through eight weekly small-group sessions and structured daily practice. MBCT studies have shown neural changes correlated with psychological wellbeing. We hypothesized that MBCT, modified to incorporate aspects relevant to persistent distressing visual symptoms, can improve symptoms by modulating dysfunctional neural pathways, training attention, and developing psychological resilience to cope with symptoms.

Objective: To assess the feasibility of modifying MBCT for visual symptoms (MBCT-vision), to treat VSS and/or persistent photophobia.

Method: Prospective cohort open-label 8-week MBCT-vision treatment trial. Quantitative (baseline, week-9, week-20): changes in self-rated 10-point-scale of symptom severity, impact on daily life, World Health Organisation Wellbeing index (WHO-Wellbeing), CORE-10 psychological distress scale, Five Facet Mindfulness Questionnaire (FFMQ). Qualitative: thematic analysis of focus-group (week-9) and questionnaire (baseline, week-9, week-20) using the Framework approach.

Results: Jan-May2020: Seven participants (6 VSS, 1 photophobia) completed the study, one (VSS) dropped out due to work. Self-rated symptom severity improved: baseline (mean 6.33, SD 1.75) to week-9 (mean 5.83,SD 2.14, p=0.45) and week-20 (mean 3.33, SD 2.16, p=0.01). Impact of symptoms improved: baseline (mean 5.5, SD 2.17) to week-9 (mean 3.67, SD 1.21, p=0.14) and week-20 (mean 1.67, SD 1.63, p=0.028). No statistically-significant change of WHO-wellbeing, CORE-10 and FFMQ scores between baseline, week-9, week-20. There were trends of improvements in FFMQ, specifically in three domains ('observing', 'acting-in-awareness', 'non-reactivity'), but did not reach statistical-significance. Thematic analysis: improved symptoms and reduced distress associated with ability to modulate attention, emotion and response to residual symptoms.

Interpretation: MBCT-vision significantly improves severity and daily impact of visual symptoms at 3-months. The trends of improvements in some mindfulness domains are of interest. The overall wellbeing and mindfulness scores may have been affected by the COVID19 pandemic. The visual improvement at 3-months compared to immediately following completion of MBCT-vision study suggests a longer period of regular mindfulness practice is needed to change neuronal pathways for symptom improvement. Future studies planned to include functional imaging will further elucidate this.

Pain Mechanisms & Treatment

240. Elevated Dietary Omega-6 Fatty Acids Exacerbate Mechanical and Cold Hypersensitivity in Diabetic Neuropathy

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Chronic pain is the leading cause of disability worldwide and commonly associated with comorbid disorders; however, the role of diet in chronic pain is poorly understood. Of particular interest is the Western-style diet, enriched with omega-6 polyunsaturated fatty acids (PUFAs) that accumulate in membrane phospholipids and oxidize into pronociceptive oxylipins. We have previously shown that mice administered a diet high in omega-6 PUFAs (H6D) develop persistent nociceptive hypersensitivities, spontaneously-active and hyper-responsive glabrous afferent fibers, and histologic markers of nerve damage indicative of peripheral neuropathy. Following H6D, linoleic and arachidonic acid accumulate in lumbar dorsal root ganglia and glabrous hindpaw, with increased liberation via elevated PLA2 activity. Based on these findings and prior association of oxidized lipids with painful diabetic neuropathy, we tested whether dietary omega-6 PUFAs affect sensory responses in db/db mice and if the neuropathic hypersensitivity previously shown in these mice could be prevented or reversed through dietary intervention with omega-3 PUFAs (H3D) or by inhibiting peripheral release of PUFAs. In this study, we identified that db/db mice fed a H6D develop significantly elevated and persistent mechanical and cold nociception beyond that of normal chow or a control low omega-6 diet. We also show that H3D prevents the development of hypersensitivity, while inhibition of a sensory-neuron-specific PLA2 reverses neuropathic hypersensitivities. Finally, we show in a cohort of diabetic patients, that omega-6 levels in peripheral punch biopsies significantly correlate with sensory testing and self-reported pain scores. Collectively, these data suggest that dietary levels of omega-6 fatty acids might act as a risk factor and biomarker for painful diabetic neuropathy, and that intervening through dietary modification or prevention of omega-6 release from peripheral membranes may provide novel approaches for clinical pain management.

241. Improvement in Pain and Physical Function Following Subcutaneous Tanezumab Treatment in Patients with Osteoarthritis

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Objective: To assess improvement in the co-primary endpoints of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain and Physical Function and Patient's Global Assessment of Osteoarthritis (PGA-OA) in 3 double-blind, parallel-group, phase 3 studies of tanezumab vs comparators.

Background: Tanezumab, a monoclonal antibody against nerve growth factor, is in development for the management of osteoarthritis (OA).

Design/Methods: Study 1 (NCT02697773) and Study 2 (NCT02709486) enrolled patients with moderate-to-severe OA pain of the knee or hip and a history of insufficient pain relief or intolerance to acetaminophen, oral nonsteroidal anti-inflammatory drug (NSAID), and either tramadol or opioids (or unwilling to take opioids). Study 3 (NCT02528188) included patients on a stable dose of NSAID prior to enrollment. Patients were randomized to tanezumab 2.5 mg or 5 mg, administered subcutaneously every 8 weeks and either placebo (Studies 1 and 2) or oral NSAIDs twice daily (Study 3). Co-primary endpoints were assessed at Weeks 16 or 24 and all studies had a 24-week safety follow-up period.

Results: In total, 4541 patients were evaluated. Study 1 met all 3 co-primary endpoints for tanezumab 2.5 mg or tanezumab 2.5 mg titrated to 5 mg vs placebo at Week 16. In Study 2, tanezumab 5 mg significantly improved all co-primary endpoints at Week 24. Tanezumab 2.5 mg met 2 co-primary endpoints but was not significant for PGA-OA. In Study 3, tanezumab 5 mg (but not 2.5 mg) produced significant improvements in WOMAC Pain and Physical Function (but not PGA-OA) at Week 16 compared with NSAID. Adverse events in tanezumab-treated patients were not notably different across studies.

Conclusion: Consistent improvements in WOMAC Pain and Physical Function were observed for 2 doses of tanezumab (2.5 mg and 5 mg) vs placebo at Weeks 16 and 24. Compared with NSAID, tanezumab 5 mg (but not 2.5 mg) significantly improved WOMAC Pain and Physical Function at Week 16.

242. Subcutaneous Tanezumab versus NSAID for the Treatment of Osteoarthritis: Neurological Safety in a Randomized, Double-Blind, Active-Controlled, 80-Week Phase 3 Study

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Background: Tanezumab, a monoclonal antibody against nerve growth factor, is in development for the relief of signs and symptoms of moderate-to-severe osteoarthritis (OA) in adult patients for whom use of other analgesics is ineffective or not appropriate.

Objective: To evaluate the long-term neurological safety of subcutaneous (SC) tanezumab treatment versus oral nonsteroidal anti-inflammatory drugs (NSAIDs).

Design/Methods: The study included patients with moderate-to-severe hip or knee OA pain and functional disability. Patients were required to have a history of inadequate pain relief with acetaminophen; inadequate pain relief with or intolerance to tramadol or opioids; or an unwillingness to take opioids. Patients were on stable doses of NSAIDs before study entry and during a ≤37-day screening period. Patients were randomized to double-dummy tanezumab (2.5 mg or 5mg, SC every 8 weeks) or twice daily NSAIDs for 56-weeks, with a 24-week follow-up. Neurological safety was assessed with peripheral and sympathetic adverse events (AEs), neurologic examinations, orthostatic blood pressure, electrocardiograms and protocol-specified neurologic consultations with blinded, external neurologist diagnostic reviews.

Results: Neurological safety was analyzed in a total of 2,996 patients. During the treatment period, the incidence of AEs of abnormal peripheral sensation (APS) was 6.2%, 9.0% and 4.6% in the tanezumab 2.5 mg, 5 mg and NSAID groups, respectively. Hypoesthesia, paresthesia and carpal tunnel syndrome were the most commonly reported AEs of APS. Clinically significant worsening on examination occurred in <1% of any treatment group at last study assessment. Diagnoses following external neurological consultation included mononeuropathy (1.3%, 2.1% and 1.0% in tanezumab 2.5mg, 5mg and NSAID groups, respectively), radiculopathy (0.9%, 0.4% and 0.5%) and polyneuropathy (0.3%, 0.5% and 0%). The incidence of AEs of possible sympathetic function (bradycardia, syncope, orthostatic hypotension, anhidrosis and hypohidrosis) was 1.8%, 2.3% and 2.9% in tanezumab 2.5mg, 5mg and NSAID groups, respectively. No patient was diagnosed with sympathetic neuropathy.

Conclusion: Increasing doses of tanezumab were associated with a higher incidence of AEs of APS than NSAIDs, primarily paresthesia, hypoesthesia and carpal tunnel syndrome. The results of external neurological consultations do not indicate that tanezumab is associated with peripheral polyneuropathy. AEs of possible decreased sympathetic function were balanced across treatment groups and there was no evidence of sympathetic nervous system dysfunction from tanezumab.

243. Worldwide Frequency of Phantom Limb Pain in People with Amputations: A Systematic Review and Meta-Analysis

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Introduction: Phantom limb pain (PLP) is a well-known but not totally understood chronic pain condition with deleterious consequences on the quality of life. Although it has been reported to be highly frequent among amputees, epidemiological data including associated protective and risk factors varies among studies based on the region, setting, design among other factors. A clear epidemiological profile of this condition will help in the decision-making process for physicians, researchers, and health policymakers.

Aim: To systematically search and determine the worldwide frequency of PLP in people with amputations.

Methods: We conducted a systematic review and meta-analysis. For this purpose, we searched in PubMed, Web of Science, Embase, and Psycinfo databases for observational studies on PLP with no language restrictions until April 4th, 2020. The articles and the data were selected by four calibrated researchers with a fifth researcher to solve discrepancies. We performed meta-analyses by a random-effects model, adjusting by Freeman-Turkey double arcsine transformation. Sensitivity analysis was carried according to relevant studies characteristics.

Results: We included 67 observational studies (n=18 360); most of the studies were cross-sectional and institution-based from high-income countries. The most common amputation cause was vascular disease associate with Diabetes Mellitus. The frequency of PLP ranged from 0% to 99%, the pooled estimate was 68% (95% CI: 58.23-77.20) with high statistical between-studies heterogeneity (I^2=97%). The frequency was not different between sex, amputation level, or localization (lower versus upper limb). Publication bias was not found in the analysis.

Conclusions: The PLP presence in people with amputation is very frequent (around 68%), without difference among cause, localization, or level of amputation. We identified high heterogeneity between studies and significant methodological limitations (lack of population-based studies). Further longitudinal studies to assess the changes of this condition across time and its associated factors are needed. These insights are critical to developing better treatment strategies.

244. Facial Pain Caused by a Traumatic Inferior Alveolar Nerve Neuroma Detected after Exploratory Surgery Despite Normal Imaging Findings

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Background: Traumatic neuromas of the inferior alveolar nerve are uncommon pseudo-tumors that can present after maxillofacial surgery. The most common symptom is neuralgic pain secondary to compression. Our case highlights the importance of taking an accurate history to guide the diagnosis and management of this condition despite normal imaging findings.

Case Presentation: A 75-year-old woman presented with a chief complaint of worsening facial pain involving the left mandibular area, which started four years ago as numbness and dull pain after she had root canal treatment. In time, the pain intensified and was triggered by light touch to her face. Physical exam was unremarkable except for decreased sensation to light touch in the left V3 distribution. MRI brain, MRA head and neck, and MR neurography did not show any abnormalities. Based on her history and despite normal imaging findings, exploratory surgery was planned and showed a 1.8 x 0.2 x 0.2 cm inferior alveolar nerve neuroma. After resection of the neuroma and repairing of the nerve, her pain subsided, and her numbness is gradually improving.

Discussion: Traumatic neuromas are uncommon entities that can occur at any age, with an estimated incidence of 0.07-0.09%. They develop after compression and stretching of nerve fibers, more commonly during root canal surgeries or maxillofacial procedures. This traumatic manipulation then leads to reactive hyperplasia over the next days to weeks, which manifests as neuropathic pain and hypoesthesia of the innervated region. Diagnostic methods include panoramic X-rays, CT, and MRI of the face. Nerve-sparing surgical excision is the treatment of choice. A recent study showed that high-resolution MRI had a sensitivity of 94% to detect structural abnormalities of the IAN (Makoto et al., 2011). In the case presented, an older woman complained of facial numbness and pain that started after root canal therapy. She had an MRI that did not show any abnormalities that could explain her symptoms. However, exploratory surgery was performed on the premise that a traumatic injury of the IAN caused her symptoms. Recent studies have reported no recurrence of pain or mass at least within three years since surgery (Tekanori et al., 2016).

245. Case Report: Stroke and Status Epilepticus as Complications of Lumbar Epidural Steroid Injection; a Cascade of Catastrophe

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Objective: The demonstration of cerebral venous thrombosis stroke and status epilepticus as previously unrecognized complications of a lumbar epidural steroid injection.

Background: Lower back pain (LBP) affects up to 84% of adults over a lifetime. Therapies include non-pharmacologic, pharmacologic, non-surgical interventional, and surgical interventional treatments. Epidural steroid injection (ESI) use has increased dramatically, rising about 5% per year between 2000-2014. A 2014 FDA Drug Safety Communication warning for ESIs cautioned that "the effectiveness and safety of the drugs for this use have not been established" and could result in serious neurological adverse events, "including loss of vision, stroke, paralysis, and death." Although stroke has been previously well described associated with cervical ESI,

we report a case of stroke and status epilepticus following a lumbar ESI.

Case: A 37-year-old man with chronic LBP received his second L5-S1 interlaminar ESI using triamcinolone and lidocaine at the L5-S1 level under fluoroscopy complicated by immediate generalized pain and lower extremity weakness which improved over 1-2 hours. A resulting post-procedural severe orthostatic headache persisted for days. On day three post procedure, he awoke with right upper extremity weakness, numbness, and paresthesias, sparing his face and legs. Within hours, the patient experienced four generalized seizures, with semiology noted as admixed right arm clonic activity. Seizure cessation occurred only after infusion of multiple antiepileptic medications, intubation and propofol sedation. Imaging revealed a left parietal infarction and an adjacent vein of Trolard cortical venous thrombosis. A dense right arm monoparesis and sensory deficits were noted on extubation, but have nearly resolved over a period of months and he has been seizure-free on medication.

Discussion: Accidental penetration of the CSF space is a known risk for lumbar ESI, while intracranial hypotension is a known risk factor for cerebral venous thrombosis. Seizures and status epilepticus are known complications for cerebral venous thrombosis infarctions. We described a cascade of complications originating from a lumbar ESI that sequentially included unintended penetration into the subarachnoid space, intracranial hypotension manifested as a post lumbar puncture headache, secondary cortical vein cerebral venous infarction, and status epilepticus arising from the region of venous infarction.

Conclusions: A cerebral venous thrombosis infarction and subsequent seizures or status epilepticus may arise as a consequence of a common complication of lumbar ESI, unintended penetration of the CSF space.

Regenerative Medicine

139. New Ferritin-Based Tissue-Specific Genetic Vectors for MR Visualization of Neurogenesis

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Introduction: Neurogenesis is considered to be a potential mechanism for brain recovery in neurodegenerative and cerebrovascular diseases. Neurogenesis in pathological conditions is a complex process that evolves over time and includes migration of young neurons from neurogenic niches to the lesion site as well as formation of new neurogenic niches. Significant increase in neurogenesis were found in the animal models of stroke and trauma. This opens new possibilities for therapy. It is difficult to reconstruct the neurogenesis process only from the histological sections taken from different animals on different stages of brain damage and restoration. Study of neurogenesis would greatly benefit from development of the tissue-specific visualization probes.

Purpose: The aim of this work was to explore if overexpression of ferritin, a nontoxic iron-binding protein, under a specific promoter can be used for non-invasive visualization of neurogenesis using magnetic resonance imaging (MRI).

Methods: Two new genetic constructs were developed based on lentiviral and (LV-pDCX-eGFP-T2a-FerrH) and adeno-associated (AAV-pDCX-FerrH) viral backbones. Both vectors contained genetic sequence of heavy chain of ferritin (FerrH) under promoter of doublecortin (DCX) that is specific for young neurons. Besides, LV construct contained the eGFP to control expression using histology. Another LV vector for ferritin overexpression under non-specific promoter (LV-pCMV-eGFP-T2a-FerrH) was used as a control. The vectors were injected to adult male Sprague-Dawley rats intracerebrally to neurogenic subventricular zone (SVZ). 14 days after injection, the animals were transcardially perfused, fixed in formalin; then T2 and T2* weighted brain images were obtained ex vivo using Philips Achieva 1.5T scanner. After imaging, brain sections were immunostained with antibodies to ferritin and DCX.

Results: ex vivo T2 images showed MRI signal hypointensity in the site of injection in the cortex and in the SVZ, in both hemispheres for AAV-pDCX-FerrH, and in ipsilateral hemisphere for LV-pCMV-eGFP-T2A-FerrH and LV-pDCX-eGFP-T2A-FerrH. Immunostaining for ferritin and eGFP fluorescence showed that injection of all vectors causes expression of the reporter genes in the neurogenic SVZ. The percentage of young neurons expressing ferritin was 93.5% for AAV-pDCX-FerrH, 63.8% for LV-DCX-eGFP-T2A-FerrH, and 63.2% for LV-CMV-eGFPT2A-FerrH.

Conclusions: Ferritin expression was detected with MRI in neurogenic subventricular zones of rat brain 2 weeks after injection of newly developed genetic constructs that was confirmed by immunochemistry. Additional studies are needed to investigate these constructs using high-field MRI and to clarify their tissue-specific features.

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140. m^{6}A Methylation Defect in Schwann Cells Impairs Myelination and Peripheral Nerve Regeneration

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N6-methlyladenosine (m6A), the most common internal modification found in eukaryotic mRNAs, is known to be a key part of developmental and regulatory processes across a

variety of cell systems. However, a role in the peripheral nervous system, particularly in peripheral glia, is yet to be described. In this study, we demonstrate that m6A patterning in Schwann cells is necessary for proper myelination during development, as well as successful recovery from nerve injury. Using a mouse model with a Schwann cell-specific conditional knockout for Mettl14, an essential component of the m6A writer complex, we first sought to describe the phenotype of these mice, which show significantly reduced neuromuscular function beginning at four months of age. Specifically, effected mice exhibit tremor, ataxia, altered gait, and loss of limb muscle strength, with increasing severity over time. Along the same timeline, we observed progressive loss of axon population, and reduced axon diameter and myelin thickness in sciatic nerve. While *in vivo* phenotypic effects were not evident until four months of age, Schwann cells purified from knockout animals showed significant *in vitro* defects when harvested from P1-P3 pups, suggesting that the loss of m6A patterning has an early effect on proper glial cell function. In addition to these developmental effects, Mettl14-KO mice also exhibited impaired nerve regeneration following crush injury. We did not observe any alterations to the degenerative program at either two- or four-months of age (i.e. normal debris accumulation), but four-month old Mettl14-KO mice showed significantly reduced density of regenerating myelinated axons at both one and two weeks post injury as well as impaired functional recovery. Cell type specific transcriptional changes are known to play a significant regulatory role in nervous system regenerative programs, and our findings suggest that m6A patterning may be a key component in Schwann cell responses to peripheral nerve injury. Together, our results establish an important role for m6A modifications to mRNA in the development and regeneration of the peripheral nervous system.

K-584. **Active Demethylation Of Genes Within Subventricular Zone Cells Following Perinatal Hypoxic-ischemic Injury May Promote Neurogenesis**

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Background/Objectives: Perinatal hypoxic-ischemic injury (HI) is a leading causes of childhood neurologic disability. While the brain can recover to some degree following injury, the extent to which this occurs is often limited. Neurogenesis is one mechanism by which the brain recovers after injury. Neural progenitor cells residing within the subventricular zone proliferate after injury and migrate to the site of injury where they can provide trophic support to the healing brain as well as differentiate and integrate into local circuitry. This activation is triggered by an upregulation of specific growth factors following injury. We aimed to regulatory role of DNA methylation this response following perinatal HI.

Methods: We induced perinatal HI in 10 day old C57BL/6 pups by ligation of the right common carotid artery followed by exposure to hypoxia (8% O_2/92% N_2) for 45 minutes. The pups were sacrificed at 4 or 24 hours for molecular biology or immunohistochemistry. We used quantitative RT-PCR to study gene expression of GADD45 family and TET family proteins. We evaluated *in situ* DNA modifications using immonhistochemistry. We also investigated global DNA methylation using dot blot analysis. Gene level methylation status was analyzed by methylation specific PCR and more broadly by reduced representation bisulfite sequencing. Finally we used thymidine analog incorporation assays with 5-ethinyl-2-deoxyuridine in *Gadd45b* knockout mice compared to wild-type controls.

Results: *Gadd45* family mRNA is rapidly upregulated by 14-fold in the subventricular zone (SVZ) by 4 hours following perinatal HI, and remains upregulated at 24 hours. Small transient increases in expression were seen for *Gadd45a* and *Gadd45g* at 4 hours. There is no significant change in the expression of TET1-3. Dot blot analysis demonstrated no difference in global levels of DNA methylation or hydroxymethylation at 24 hours, but preliminary results for *BDNF* suggest specific demethylation of the *BDNF* promoter by 24 hours. Immunohistochemistry revealed increased expression of 5-hydroxymethylcytosine specifically within the SVZ progenitor cells. Knockout of Gadd45b resulted in reduced numbers of proliferating SVZ progenitor cells despite comparable degrees of injury.

Conclusions: Perinatal HI induces upregulation of *Gadd45b*, which may contribute to demethylation of growth promoting genes in the neurogenic niche and underlie the activation of neural stem and progenitor cells following injury. Understanding which genes are effective may allow development of epigenetically-targeted therapies to influence this response.

Sleep Disorders and Circadian Rhythm

429. The Circadian Protein Bmal1 Mediates Cell Type-Specific Effects on Protein Aggregation and Neuronal Survival in Mouse Models of Synucleinopathy and Tauopathy

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Circadian dysfunction is a common but poorly understood symptom of most neurodegenerative diseases. Deletion of the master circadian clock transcription factor *Bmal1* abrogates cellular circadian clock function and can be used to query cell type-specific functions of the clock. We have previously shown that global *Bmal1* deletion induces oxidative stress, neuronal damage, astrocyte activation, and amyloid-beta plaque deposition in mice. Here we investigated the effect of cell type-specific *Bmal1* deletion in a model of alpha-synuclein (aSyn) pathology using injection of aSyn preformed fibrils (PFFs). Global *Bmal1* deletion prior to intrastriatal aSyn PFF injection induced astrocyte activation and

unexpectedly inhibited accumulation of aSyn pathology in multiple brain regions. Astrocyte-specific deletion of *Bmal1*, which induces cell-autonomous astrocyte activation, also protected against aSyn pathology in this model. Conversely, global *Bmal1* deletion resulted in loss of tyrosine hydroxylase-positive dopaminergic neurons in the substantia nigra pars compacta, which was further exacerbated by striatal aSyn PFF injection. This dopaminergic neuron loss was recapitulated by neuron-specific, but not by astrocyte-specific *Bmal1* deletion. Finally, we examined global post-natal deletion of *Bmal1* in a P301S tau transgenic mouse model, and again observed early astrocyte activation as well as a marked decrease in the accumulation of insoluble tau aggregates and neuroinflammation. Our findings demonstrate that the core circadian clock regulates distinct pathways in neurons and astrocytes, and that targeting the astrocyte clock to induce early activation may be a novel therapeutic strategy for aSyn and tau-related neurodegenerative diseases.

430. A Correlational Meta-Analysis Investigating Sleep Quality and Episodic Memory Performance at the Behavioral and Neural Level in Young and Older Adults

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Previous research demonstrates that sleep is critical for episodic memory performance in young adults. However, the strength of the relationship between sleep quality and episodic memory performance in older adults has not been well characterized. It is clear that older adults experience greater sleep disturbance and reduced N3 (i.e., slow wave sleep) as compared to young adults. Such changes in sleep quality could negatively impact episodic memory performance. However, the research on whether older adults demonstrate relationships between sleep quality and episodic memory is mixed. Apart from age, other factors could moderate sleep-memory associations. For example, it is unclear whether certain sleep measurement methods (e.g., polysomnography, actigraphy, or self-report) or sleep parameters (e.g., slow wave sleep, sleep duration) modulate the strength of sleep-memory associations. The strength of sleep-memory associations could also differ by episodic memory task characteristics (e.g., verbal vs pictorial stimuli) or memory phase (e.g., immediate vs delayed retrieval). Furthermore, underlying neural correlates of episodic memory, such as memory-related functional brain activity and amyloid beta burden, have been associated with sleep quality measures, but it is currently unknown if the magnitude of these associations differ by neural measure. Thus, the present meta-analysis assessed if the aforementioned factors modulated sleep-memory associations at the behavioral and neural level. We searched for independent studies with cognitively healthy adults where individual differences for sleep quality and episodic memory performance and/or sleep quality and memory-related neural measures (functional, structural, amyloid beta burden) were reported. Across all behavioral measures and age groups, we found no significant differences in the strength of sleep-memory associations for polysomnography, actigraphy, or self-report. Furthermore, young and older adults had similarly strong, positive associations between sleep quality and episodic memory performance. However, when we further assessed specific sleep quality moderators (across all memory measures), older adults had stronger sleep-memory associations for sleep disturbance (i.e., wake after sleep onset), and young adults had stronger sleep-memory associations for stage N3 (i.e., slow wave sleep). At the neural level, young adults had stronger associations for sleep quality and functional brain activity than older adults. In brief, the present meta-analysis demonstrates that young and older adults maintain similar relationships between sleep quality and episodic memory performance. However, these groups differ in sleep-memory associations for sleep disturbance, slow wave sleep, and functional brain activity.

431. Effects of Solriamfetol on Driving Performance in Participants with Narcolepsy

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Introduction: Patients with narcolepsy have an increased risk of automobile accidents. Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, is approved in the US and EU (Sunosi®) to improve wakefulness in adult patients with excessive daytime sleepiness (EDS) associated with narcolepsy. The approved dose range is 75 to 150 mg once daily. This study evaluated the effects of solriamfetol on on-road driving performance in participants with narcolepsy.

Methods: In each period of this randomized, double-blind, placebo-controlled, crossover study (NCT 02806908; EudraCT 2015-003931-36), driving performance during an on-road driving test (1-hour drive on a public highway) was assessed at 2 hours and 6 hours post-dose following 7 days of treatment with solriamfetol (150 mg/d for 3 days, followed by 300 mg/d for 4 days) or placebo. For assessment of driving performance, the primary endpoint was standard deviation of lateral position (SDLP), a measure of "weaving" (departure from a steady lane position), at 2 hours post-dose. Wilcoxon signed-rank test was used for comparisons between solriamfetol and placebo.

Results: The study included 24 participants (54% male; mean age, 40 years); 22 were included in the analyses of SDLP. At 2 hours post-dose, median SDLP was statistically significantly lower for participants treated with solriamfetol versus placebo (19.08 vs 20.46 cm; P=0.0022), indicating better driving performance with solriamfetol. At 2 hours post-dose, 4 participants receiving solriamfetol and 7 participants receiving placebo failed to complete the driving test. At 6 hours post-dose, the median SDLP for solriamfetol was not statistically different from that for placebo (19.59 vs 19.78 cm; P=0.1245). At 6 hours post-dose, 3 participants receiving solriamfetol and 10 participants receiving placebo failed to complete the driving test. Common adverse events (≥5%) were headache, decreased appetite, somnolence, sleep disorder, agitation, nausea, and palpitations.

Conclusion: Solriamfetol (300 mg/d) improved SDLP, an important measure of driving performance, at 2 hours after administration in participants with narcolepsy.

432. Alcohol Dependence as Enantiopathy to Cataplexy

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Introduction: Use of alcohol to reduce anxiety/induced cataplexy in a narcoleptic with the unintended consequence of alcohol dependence has not heretofore been described.

Case Study: A 47-year-old right-handed male noted that while as a freshman in high school, he would easily fall asleep during class. This persisted and worsened to the point that he fell asleep more than five times per day, despite his attempts to remain awake and would even occur during enjoyable and entertaining events. Furthermore, upon awakening, he was unable to move for several seconds. He frequently experiences sagginess of his jaw, coincident with the experience of strong emotion. When he became upset, he would fall down, asleep, primarily precipitated by anxiety. These episodes of falling down would occur 8 to 10 times a day, depending upon his emotional state. As a result, he would avoid emotions that would precipitate this, such as laughter, frustration, anger and excitement. For instance, if given a surprise party, when the guests yelled "surprise" or when told particularly humorous jokes, he would become atonic and fall to the floor, asleep. Moreover, his father had a diagnosis of narcolepsy. At age 16, he began to drink alcohol and found that after acute consumption his anxiety would be markedly reduced and his cataplectic attacks would subside. He continued to use alcohol every day, gradually increasing the amount, up to eight shots of whiskey each day. He has been arrested in the past for driving under the influence of alcohol. His drinking has persisted despite treatment with Alcoholics Anonymous, naltrexone, and multiple hospitalizations for withdrawal.

Results: Abnormalities in physical examination: Neurologic examination: Motor examination: Drift testing: left pronator drift. Gait: unstable tandem gait. Multiple Sleep Latency test: positive (narcolepsy) Swiss Narcolepsy Scale: -2 (narcolepsy) (Bargiotas, 2019).

Discussion: While the development of dependence on alcohol in a narcoleptic with cataplexy is an understandable extension of its anxiolytic effects, alcohol dependence in narcoleptics is not the usual situation (Wang, 2012). In this patient, the severe anxiety sensitivity of the cataplexy and the anxiolytic effects of alcohol, must have superseded its somniferous properties, but with chronic use, culminated in dependence. This suggests that for those with cataplexy and alcohol dependence, treatment with anxiolytics may be beneficial.

433. Cataplexy-Free Days during Sodium Oxybate Treatment in Children and Adolescents with Narcolepsy with Cataplexy

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Introduction: Sodium oxybate (SXB) is approved for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. A placebo-controlled, double-blind, randomized withdrawal study established the efficacy and safety of SXB in pediatric patients 7-17 years of age. The objective of this analysis was to determine the number of cataplexy-free days/week experienced by participants treated with SXB in this clinical trial.

Methods: SXB-naive participants were titrated to an optimal dose of SXB and then entered a stable-dose period (SD) for 2 weeks; participants already taking SXB entered SD on their usual dose of SXB for 3 weeks. After a 2-week, placebo-controlled, double-blind, randomized withdrawal period (DB), participants entered an open-label safety period (OL) for a total duration of ≤1 year. Cataplexy-free days/week were calculated from daily participant diaries.

Results: Of 106 participants, 74 (69.8%) were SXB naive and 32 (30.2%) were taking SXB at enrollment. In SXB-naive participants, median (Q1, Q3) cataplexy-free days/week increased during titration: week 1 (0.0 [0.0, 2.0]), week 2 (1.0 [0.0, 3.0]), and last 7 days (4.0 [1.0, 6.0]); n=71. Sixty-seven SXB-naive participants entered SD. During the last 14 days of SD, cataplexy-free days/week remained stable and were similar in participants who had been SXB naive or taking SXB at study entry: 4.3 (1.0, 5.8), n=66, and 4.8 (0.8, 6.5); n=32, respectively. During the last week of DB, cataplexy-free days/week decreased to 0.0 (0.0, 2.7) in participants randomized to placebo (n=32) but remained stable at 4.0 (1.0, 6.0) in participants continuing SXB (n=31). During the last week of observation for each participant in the OL period, median cataplexy-free days/week was 5.0, both in participants who had been SXB naive (n=63) and in participants taking SXB at study entry (n=32). Common adverse events (>10%) in the safety population (n=104) were enuresis, nausea, vomiting, headache, and decreased weight.

Conclusions: The number of cataplexy-free days/week increased with SXB treatment in children and adolescents with narcolepsy with cataplexy. The overall safety profile observed in this study was consistent with previous adult and pediatric narcolepsy studies.

Previous Presentation: SLEEP 2019, the 33rd Annual Meeting of the Associated Professional Sleep Societies; June 8-12, 2019; San Antonio, TX; Poster 266.

434. Sodium Oxybate Treatment Effects on Sleep Architecture in Pediatric Patients with Narcolepsy with Cataplexy

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Introduction: Sodium oxybate (SXB) is approved for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. A placebo-controlled, double-blind, randomized withdrawal study established the efficacy and safety of SXB in pediatric patients 7-17 years of age (Part 1, ≤1 year). An open-label (OL) safety study (Part 2) provided SXB treatment for up to 2 additional years. The objective of this analysis was to report the effects of SXB on sleep architecture in the pediatric study of participants with narcolepsy.

Methods: Participants with narcolepsy with cataplexy (7 −16 years of age at screening) were eligible. SXB-naive participants were titrated to an optimal SXB dose and entered a 2-week stable-dose period (SD). Participants already taking SXB entered the SD at their optimal dose. After the SD, participants were randomized to take placebo or continue SXB treatment in a 2-week, double-blind, randomized withdrawal period (DB), then all participants entered OL treatment for up to 47 weeks (Part 1). SXB-naive participants underwent polysomnography during screening (before initiating SXB), end of the SD (optimal dose), and end of Part 1 (optimal dose). Participants taking SXB at study entry underwent polysomnography at screening and end of Part 1 (both times taking their usual dose of SXB).

Results: Of 106 participants, 85 completed Part 1. In SXB-naive participants, changes from screening to end of the SD included arousals/night (median [Q1, Q3] change, −43.0 [−58.0, −17.0]) and percentage of time in non-rapid eye movement (non-REM) stage 1 sleep (N1%; −4.6% [−7.5, −0.6]) and non-REM stage 3 sleep (N3%; 12.6% [7.1, 20.9]). These changes were maintained through the end of Part 1. In participants taking SXB, sleep architecture remained similar from screening to end of Part 1. Treatment-emergent adverse events (TEAEs) >10% during Part 1 were enuresis, nausea, vomiting, headache, and decreased weight. TEAEs with onset in Part 2 in >2 participants were upper respiratory tract infection and nasopharyngitis. Increased mean blood pressure was observed in Part 2; however, blood pressure and other vital signs generally remained within normal range throughout the study.

Conclusions: Open-label SXB treatment in children with narcolepsy was associated with reduced arousals, reduced light sleep, and increased deep sleep. Treatment effects and TEAEs were consistent overall with those in studies in adults.

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435. Non-Invasive Calcium Imaging Reliably Classifies Sleep States

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Introduction: In mammals waking and various stages of sleep can be defined based on electroencephalography because it provides an objective and functional marker of sleep, but is often invasive, suffers from volume conduction and lacks spatial resolution. Therefore a non-invasive, high spatial resolution methodology to monitor neuronal activity during sleep is needed. Recently, we have developed a wide-field calcium-imaging platform using a genetically encoded calcium indicator (GECI) that allows non-invasive, serial imaging of the neuronal activity of the cortex. The purpose of this study is to evaluate whether wide-field calcium imaging can reliably discriminate wake from sleep.

Methods: To assess sleep in living mice we fitted four transgenicThy-1-GCaMP6f mice with chronic plexiglass cranial windows and traditional EEG screws. After adapting to head fixation, mice were given a 3 hour opportunity to sleep while undergoing simultaneous whole cortex calcium imaging and electroencephalography. Sleep was scored offline based on traditional EEG rules in 10 second epochs. To classify sleep based on calcium imaging a set of features (delta power 1-4 Hz, whole spectra power, slow oscillation identification and homeostatic decline of delta power) were identified.

Results: Mice were able to reliably sleep in head fixation (47% Wake, 47% NREM, 6% REM). Analysis of the GCaMP6 signal revealed increases in delta power aligned with NREM and decreases with REM sleep. GCaMP6 NREM delta power homeostatically decreased across the sleep period. Topographic spatial analysis revealed a NREM specific increase in anterior regions that was absent in REM. Finally, GCaMP6 delta power was a reliable indicator of sleep states and was tightly coupled to EEG-based cortical activity.

Conclusions: With the high spatial resolution of wide-field calcium imaging, we can reliably and non-invasively classify sleep states on the calcium signal alone. This provides a viable alternative to electroencephalography and will allow sleep-based wide-field studies on cortical network organization, plasticity and neurological disease.

436. Efficacy and Safety of JZP-258 in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study in Adults with Narcolepsy with Cataplexy

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Introduction: Sodium oxybate (SXB) is approved to treat cataplexy and excessive daytime sleepiness (EDS) in patients with narcolepsy. JZP-258 is an oxybate product candidate with 92% less sodium. The objective of this study was to evaluate the efficacy and safety of JZP-258 in adults with narcolepsy with cataplexy.

Methods: Enrolled participants were 18-70 years of age with narcolepsy with cataplexy. JZP-258 treatment began with a 12-week, open-label titration and optimization period, followed by a 2-week, open-label stable-dose period (SDP). Participants were then randomized to placebo or continued JZP-258 during a 2-week, double-blind, randomized withdrawal period (DBRWP). The primary efficacy endpoint was change in average weekly number of cataplexy attacks from 2-week SDP to 2-week DBRWP. The key secondary endpoint was change in Epworth Sleepiness Scale (ESS) score; other endpoints included Patient and Clinician Global Impression of Change (PGIc, CGIc).

Results: 201 enrolled participants received ≥1 dose of JZP-258 (safety population); 134 received double-blind treatment (efficacy population: JZP-258, n=69; placebo, n=65). During DBRWP, weekly cataplexy attacks increased in participants randomized to placebo vs continuing JZP-258 treatment (median [Q1, Q3]: 2.35 [0.00, 11.61] vs 0.00 [−0.49, 1.75], respectively; $P<0.0001$). Similarly, ESS scores increased in participants randomized to placebo vs continuing JZP-258 treatment (median [Q1, Q3]: 2.0 [0.0, 5.0] vs 0.0 [−1.0, 1.0], respectively; $P<0.0001$). Narcolepsy overall worsened in more participants randomized to placebo vs continuing JZP-258 treatment (Much Worse/Very Much Worse for placebo vs JZP-258: PGIc, 44.6% vs 4.3%; CGIc, 60.0% vs 5.9%; $P<0.0001$ [nominal]). Common treatment-emergent adverse events (TEAEs) included headache (41/201; 20.4%), nausea (26/201; 12.9%), and dizziness (21/201; 10.4%). Serious treatment-related TEAEs were reported in 2 participants (confusional state and visual hallucination after unrelated accidental JZP-258 dosing error in 1 participant; muscle enzymes increased 1 day after end of placebo treatment in 1 participant).

Conclusions: Significant differences in cataplexy and EDS in this study demonstrated the efficacy of JZP-258. The overall safety profile of JZP-258 was consistent with SXB.

Previous Presentation: World Sleep; September, 20-25, 2019; Vancouver, Canada; Oral presentation 28.

437. JZP-258 Dose Titration and Transition from Sodium Oxybate in a Placebo-Controlled, Double-Blind, Randomized Withdrawal Study in Adult Participants with Narcolepsy with Cataplexy

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Introduction: Sodium oxybate (SXB) is a standard of care for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. JZP-258 is an oxybate product candidate (at same concentration as SXB) with 92% less sodium. JZP-258 dose adjustment during titration was evaluated.

Methods: At study entry, participants were taking SXB only, SXB+other anticataplectics, anticataplectics other than SXB, or were cataplexy treatment naive. JZP-258 treatment began during a 12-week, open-label optimized treatment and titration period. Participants taking SXB only or SXB+other anticataplectics transitioned to JZP-258 at the same gram-for-gram dose as SXB and titrated to an efficacious and tolerable (optimal) dose from weeks 3-12. Participants taking other anticataplectics or who were anticataplectic naive initiated JZP-258 at 4.5 g/night and were titrated to an optimal dose at 1-1.5 g/night/week (maximum total dose, 9 g/night). A 2-week stable-dose period and 2-week, double-blind, randomized withdrawal period followed.

Results: During the stable-dose period, total nightly JZP-258 dose (median [range]) was higher in participants taking SXB at study entry (SXB only, 7.5 g [4.5-9.0], n=45; SXB +other anticataplectics, 9.0 g [6.0-9.0], n=14) compared with those not taking SXB (other anticataplectics, 7.5 g [4.5-9.0], n=23; anticataplectic naive, 7.0 g [3.0-9.0], n=67), and dose adjustments were fewer. In most (69%) participants taking SXB at study entry who entered the stable-dose period, no change in dose was required (median [range] number of adjustments was 0 ([0-8]); for those with a change in dose, most changes were within one titration step (1.5 g/night). In participants not taking SXB at study entry, the median (range) number of adjustments was 3.0 (0-7).

Conclusions: Most participants taking SXB at study entry transitioned to JZP-258 treatment at the same dose with retained effectiveness. Participants not previously taking SXB achieved a tolerable and efficacious dose of JZP-258 after a median of 3 adjustments.

Previous Presentation: SLEEP 2020, the 34th Annual Meeting of the Associated Professional Sleep Societies (APSS); June 13-17, 2020; Philadelphia, PA; Poster 205.

438. Cataplexy-Free Days in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of JZP-258 in Adults with Narcolepsy with Cataplexy

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Introduction: Sodium oxybate (SXB) is a standard of care for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. JZP-258 is a novel oxybate product candidate with 92% less sodium. This analysis evaluated cataplexy-free days/week, as a measure of treatment impact, in a placebo-controlled randomized withdrawal study of JZP-258 treatment in patients with narcolepsy.

Methods: Treatment for cataplexy at study entry included 1) SXB (SXB-only); 2) SXB plus other anticataplectics (SXB +other); 3) anticataplectics other than SXB (other anticataplectics); or 4) cataplexy treatment-naive (anticataplectic-naive). Participants (aged 18-70 years with narcolepsy with cataplexy) began JZP-258 treatment during a 12-week, open-label, optimized treatment and titration period (OLOTTP), followed by a 2-week stable-dose period (SDP). Participants were randomized to receive placebo or continue JZP-258 treatment during a 2-week, double-blind, randomized withdrawal period (DBRWP).

Results: Of 201 enrolled participants, 134 comprised the efficacy population (placebo, n=65; JZP-258, n=69). Median (Q1, Q3) cataplexy-free days/week at first week of OLOTTP (while initiating JZP-258) by prior treatment were SXB-only, 5.8 (2.0, 7.0); SXB+other, 6.4 (5.0, 7.0); other anticataplectics, 4.0 (1.8, 6.0); anticataplectic-naive, 3.5 (0, 5.8). At end of SDP (on stable dose of JZP-258), median (Q1, Q3) cataplexy-free days/week were 6.0 (3.5, 7.0), 6.1 (1.4, 7.0), 6.0 (2.6, 7.0), and 6.2 (4.0, 7.0), respectively. At end of SDP, prior to randomization, there was no difference in median cataplexy-free days/week between participants to be randomized to placebo (6.0 [3.5, 7.0]) or JZP-258 treatment (6.0 [3.0, 7.0]); during DBRWP, median cataplexy-free days/week decreased in participants randomized to placebo (3.5 [0, 5.83]) but remained stable in participants randomized to continue JZP-258 treatment (5.6 [2.8, 7.0]). The overall safety profile of JZP-258 was consistent with observations in previous studies of SXB.

Conclusions: Cataplexy-free days/week were higher during week 1 of OLOTTP in participants taking SXB at study entry compared with those not taking SXB. Cataplexy remained well controlled at end of SDP in participants taking SXB at study entry. Cataplexy-free days/week increased with JZP-258 treatment in participants previously taking only other anticataplectics or naive to anticataplectics. Cataplexy-free days/week decreased during DBRWP in participants randomized to placebo but not in those randomized to continue taking JZP-258.

Previous Presentation: SLEEP 2020, the 34th Annual Meeting of the Associated Professional Sleep Societies (APSS); June 13-17, 2020; Philadelphia, PA; Poster 206.

439. Identification of a Molecular Basis for the Juvenile Sleep State

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Across species, sleep amounts are highest in young animals and decrease with age. Increasing evidence suggests early life sleep may represent a distinct behavioral state, uniquely evolved to facilitate brain structural maturation. In humans, childhood sleep disturbances portend later neurocognitive deficits and are highly prevalent across neurobehavioral disorders, possibly because sleep disruptions during development may impinge on neural circuit formation. Understanding the regulation of juvenile sleep may reveal pathogenic mechanisms and possible treatments for neurobehavioral disorders. However, while mechanisms controlling mature adult sleep have been uncovered, the molecular determinants of early life sleep remain completely unknown. Sleep in the genetically accessible fruit fly, *Drosophila melanogaster*, shares many features with mammalian sleep, including increased sleep in early life and common genetic control. Through an RNAi-based screen, we identified a gene, *pdm3*, required for sleep maturation in *Drosophila*. *Pdm3* is a POU-domain transcription factor, part of a gene family with highly conserved roles in nervous system patterning across species and links to neurodevelopmental disease in mammals. We found that in *Drosophila*, *pdm3* coordinates an early developmental program that prepares the brain to later execute high levels of juvenile adult sleep. PDM3 acts during a specific developmental window to control the wiring of wake-promoting dopaminergic (DA) neurites to a sleep-promoting region. Loss of PDM3 prematurely increases DA inhibition of the sleep center, abolishing the juvenile sleep state. RNA-Seq/ChIP-Seq and a subsequent modifier screen reveal that *pdm3* represses expression of the synaptogenesis gene *Msp300* to establish the appropriate window for DA innervation. Thus, *pdm3* is the first known genetic regulator of the juvenile sleep state. These studies provide a new platform for examining the behavioral consequences of disrupted early life sleep. The developmental role of *pdm3* in orchestrating establishment of sleep circuits raises the intriguing possibility that primary sleep disorders such as insomnia or hypersomnia may have neurodevelopmental origins. The identification of genes and circuits regulating juvenile sleep thus deepens our understanding of how sleep matures and its age-specific functions for the nervous system.

440. Validation of Actigraphy for Sleep Measurement in Children with Cerebral Palsy

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Children with cerebral palsy are frequently reported to have sleep problems, but objective assessment of sleep may be challenging. Wearable biosensors that measure movement, called actigraphs, can be used to quantify sleep in the home environment. Movement patterns differ in children with cerebral palsy and the ability of actigraphy to detect sleep has

not been studied in this population. Our goals were to validate actigraphy for sleep assessment in children with cerebral palsy and to study home sleep patterns in children with cerebral palsy using actigraphy. We recruited children with (N=13) and without cerebral palsy (N=13) aged 2-17 years who had been referred for polysomnography for clinical indications. We obtained wrist and forehead actigraphy with concurrent polysomnography for one night, and 16 participants (8 with cerebral palsy, 8 without cerebral palsy) continued home wrist actigraphy for one week. We developed novel algorithms using a weighted logistic regression model that allows for individualized sleep-wake scoring parameters. Accuracy was calculated as the percentage of actigraphy epochs in agreement with polysomnography-determined sleep versus wake staging. Our algorithms had an accuracy of 80% in children with cerebral palsy and 87% in children without cerebral palsy, with wrist and forehead locations having similar accuracy. The best window size for actigraphy analysis was longer for children with cerebral palsy than for children without cerebral palsy, signifying a pattern of less frequent movements in children with cerebral palsy. Compared to existing algorithms, our algorithms had improved specificity (64-73%), or wake detection, similar sensitivity (91%), or sleep detection, and improved overall performance. Children with cerebral palsy had worse sleep at home, with greater wake time after sleep onset (181 versus 113 minutes, p=0.04), lower sleep efficiency (60 versus 70%, p=0.17), and reduced total sleep time (355 vs 417 minutes, p=0.18) than children without cerebral palsy. Actigraphy analyzed with our algorithms provides a valid tool for assessing sleep in children with cerebral palsy or children without cerebral palsy. The improved specificity compared to existing algorithms enables better detection of sleep disruption. Further research may permit application of our algorithms for sleep assessment in children or adults with various etiologies of movement impairment and in other patient populations.

441. Long-Term Effects of Solriamfetol on Functioning and Work Productivity in Participants with Excessive Daytime Sleepiness Associated with Narcolepsy

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Introduction: Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, is approved in the US and EU to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy (approved dose range: 75-150 mg/d) or obstructive sleep apnea (OSA; approved dose range: 37.5-150 mg/d). The aim of the current analysis was to evaluate the effects of solriamfetol on measures of functioning and work productivity in a subgroup of participants with narcolepsy in a long-term open-label extension (OLE) study.

Methods: Participants with EDS associated with narcolepsy or OSA who completed previous solriamfetol studies were eligible. The long-term OLE study included a 2-week titration phase followed by a maintenance phase of ≤50 weeks (stable doses of 75, 150, or 300 mg). Assessments included the Functional Outcomes of Sleep Questionnaire short version (FOSQ-10) and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP; the specific health problem was either "narcolepsy" or "OSA"). Mean (standard deviation; SD) changes from baseline were summarized. Safety was also assessed. Data are reported for the subgroup of participants with narcolepsy.

Results: The safety population included 226 participants with narcolepsy. Increases (improvements) in mean FOSQ-10 total score from baseline (mean change [SD]: 3.7 [3.2]) were sustained for the duration of treatment with solriamfetol. On the WPAI:SHP, mean % reduction (improvement) from baseline was -26.7% for % activity impairment outside of work, -29.5% for % impairment while working (presenteeism), and -29.5% for % overall work impairment due to the problem ("narcolepsy"). Common adverse events (AEs; ≥5%) included headache, nausea, anxiety, nasopharyngitis, decreased appetite, insomnia, and dry mouth; 6 participants (2.7%) had ≥1 serious AE.

Conclusions: Solriamfetol demonstrated sustained improvements over approximately 1 year in measures of functioning and work productivity in participants with narcolepsy. The majority of AEs were mild to moderate in severity.

442. Access to Sleep Care in Patients with Mild Traumatic Brain Injury

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Objective: Sleep disturbances are prevalent in patients with mild traumatic brain injury (mTBI) in the acute period and often progress into the chronic phase. Treating sleep problems is key in the functional recovery of mTBI. While prior literature has inspected diagnosis and treatment of sleep disturbance after mTBI, little is known about access to care in this patient population. Our study aims to characterize patients with sleep disturbance post mTBI, and examine the care processes for treating sleep disturbance with the goal of improving quality of care.

Methods: This study is a retrospective investigation conducted in a large academic medical center. Electronic medical data from 2011 to 2020 are obtained from Health Data Compass (Compass), a multi-institutional data warehouse. Data include patient demographics, encounter information,

medical history, diagnoses and procedure notes. Inclusion criteria include patients age 18-64, mTBI or concussion with diagnostic codes ICD-9 Code = 850* and ICD-10 Code = S06*, and encounters in outpatient or emergency room setting. Exclusion criteria include inpatient encounters.

Results: A total of 9415 patients are identified with mTBI diagnoses, of which 2405 patients (25.54%) have sleep disturbance. 981 patients have sleep disturbance post mTBI while 1424 patients have pre-existing sleep diagnoses. Patients with sleep disturbance post mTBI are older and more likely to have various co-morbidities. 26.91% of patients with sleep disturbance post mTBI are referred to sleep medicine clinic, and 35.74% patients undergo sleep diagnostic studies. There is significant delay in seeking care for sleep disturbance in this population; on average patients are diagnosed with sleep diagnosis 501.91 days after mTBI. For patients referred to sleep medicine, referrals are made 259.22 after sleep diagnosis is made. For patients undergoing diagnostic studies, studies are performed 127.46 days after sleep diagnosis is made. These care processes are also influenced by sleep diagnoses.

Conclusion: Sleep disturbance is a common neurological problem after mTBI. The interval between diagnosis of mTBI and sleep problem needs further evaluation to determine cause. Delays in sleep diagnosis and in treatment can result in poor health outcomes. Patients who are referred to specialty sleep care could receive more timely and appropriate evaluations. Understanding care processes is first step in managing sleep disturbance to enhance functional recovery after mTBI.

443. Changes in Cataplexy Frequency by Therapy at Study Entry in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of JZP-258 in Adults with Narcolepsy with Cataplexy

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Introduction: Sodium oxybate (SXB) is a standard of care for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. JZP-258 is an oxybate product candidate with 92% less sodium. The objective of this analysis was to report cataplexy frequency during titration and optimization of JZP-258 and taper and discontinuation of other anticataplectics in a phase 3 study.

Methods: Participants (18-70 years of age with narcolepsy with cataplexy) began a 12-week, open-label optimized treatment and titration period (OLOTTP): after initial JZP258 titration (≥2 weeks), prior anticataplectics were tapered and discontinued by week 10. A 2-week stable-dose period (SDP) and 2-week, placebo-controlled, double-blind, randomized-withdrawal period (DBRWP) followed. The primary efficacy assessment was change in weekly number of cataplexy attacks from SDP to DBRWP.

Results: The safety population included 201 enrolled participants; 134 participants received randomized study treatment (efficacy population). Median (Q1, Q3) weekly cataplexy at week 1, end of OLOTTP, and end of SDP by prior anticataplectic therapy was: SXB only (n=41), 2.0 (0.0, 10.0), 1.0 (0.0, 7.0), and 1.0 (0.0, 4.0); SXB+other anticataplectics (n=14), 0.6 (0.0, 3.0), 2.2 (0.0, 31.5), and 2.0 (0.0, 23.0); other anticataplectics (n=21), 3.5 (1.0, 9.3), 2.3 (0.0, 9.0), and 2.0 (0.0, 11.2); anticataplectic naive (n=58), 5.8 (1.4, 12.6), 2.0 (0.0, 5.0), and 0.9 (0.0, 5.3). Common treatment-emergent adverse events (TEAEs) with JZP-258 included headache (41/201; 20.4%), nausea (26/201; 12.9%), and dizziness (21/201; 10.4%). Serious treatment-related TEAEs were reported in 2 participants (confusional state and visual hallucination after unrelated JZP-258 dosing error in 1 participant and muscle enzymes increased 1 day after end of placebo treatment in 1 participant).

Conclusions: In participants taking SXB only at study entry, cataplexy remained controlled with JZP-258 treatment. In anticataplectic-naive participants, cataplexy decreased with JZP-258 treatment. In participants taking other anticataplectics with or without SXB at study entry, cataplexy increased with anticataplectic taper and discontinuation, then stabilized during OLOTTP and SDP. The overall TEAE profile of JZP-258 was consistent with SXB.

Previous Presentation: World Sleep; September, 20-25, 2019; Vancouver, Canada; Poster 179.

444. Quality of Life in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of JZP-258 in Adults with Narcolepsy with Cataplexy

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Introduction: Narcolepsy negatively impacts health-related quality of life (HRQoL). Sodium oxybate is a standard of

care for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. JZP-258 is an oxybate product candidate with 92% less sodium. Efficacy and safety of JZP-258 were established in a double-blind randomized withdrawal study in adults with narcolepsy with cataplexy.

Methods: Participants 18-70 years of age began JZP-258 treatment during a 12-week, open-label, optimized treatment and titration period, followed by a 2-week stable-dose period (SDP). Participants were then randomized to receive placebo or continue JZP-258 treatment during a 2-week, double-blind, randomized withdrawal period (DBRWP). HRQoL assessments included the 36-Item Short Form Health Survey Version 2 (SF-36) and 5-level EuroQoL 5-Dimensions Self-Report Questionnaire (EQ-5D-5L).

Results: 201 participants enrolled; 134 were randomized and received at least 1 dose of double-blind study medication (efficacy population; placebo, n=65; JZP-258, n=69). Decreased scores (worsening) were observed in participants randomized to placebo compared with participants randomized to continue JZP-258 treatment for the SF-36 physical component summary (median [Q1, Q3], −1.92 [−3.46, 1.73] for placebo and −0.03 [−2.07, 2.41] for JZP-258; nominal *P*=0.02), SF-36 mental component summary (−1.92 [−6.28, 1.34] for placebo and 1.55 [−1.88, 3.78] for JZP-258; nominal *P*=0.03), and EQ-5D-5L visual analog scale (−5.00 [−10.0, 5.00] for placebo and 0 [0, 5.00] for JZP-258; nominal *P*=0.01). No change was observed in the EQ-5D-5L crosswalk index (0 [−0.05, 0.03] for placebo and 0 [−0.01, 0.03] for JZP-258; nominal *P*=0.39). The overall safety profile of JZP-258 was similar to sodium oxybate.

Conclusions: HRQoL worsened in participants randomized to placebo during DBRWP but remained stable in participants who continued JZP-258 treatment.

Previous Presentation: SLEEP 2020, the 34th Annual Meeting of the Associated Professional Sleep Societies (APSS); June 13-17, 2020; Philadelphia, PA; Poster 201.

445. Prevalence, Incidence and Chronicity of Hypersomnolence Symptoms in the General Population

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Introduction: Hypersomnolence can be very debilitating and impair several aspects of the daily life. According to the DSM5, hypersomnolence can manifest in different ways: excessive sleepiness, prolonged main sleep period, frequent naps during the day, sleep inertia, etc. Information regarding the long-term evolution of these hypersomnolence symptoms is nearly non-existent.

Methods: This longitudinal study was carried out in eight states in the U.S. A total of 12,218 subjects were interviewed by phone during the first wave (W1) and 10,930 at the second wave (W2) three years apart. The analyses included only the subjects who participated in the 2 waves (N=10,930). Hypersomnolence symptoms was assessed according to DSM-5 criteria.

Results: At W1, 27.2% of the sample had at least one hypersomnolence symptoms listed in the DSM5 occurring at least 3 days per week. This prevalence at W2 was 26.4%. The incidence of DSM5 hypersomnolence symptoms was 20.5% which represents a yearly incidence of 5.8%. Symptoms were chronic in 42.4% of cases. The chronicity increased with the number of hypersomnolence symptoms reported. It was 40.9% when only 1 symptom was reported, 46.1% when 2 symptoms were reported and 61.4% when 3 or more symptoms were reported. Over the time, the most stable individual symptoms were feeling sleepy during the daytime (37.3% of chronicity) and being sleepy or drowsy in situations demanding high attention like at work, while driving or during conversations (37.5%). For a part of the sample, a change in the type of the hypersomnolence symptoms were observed between W1 and W2. For example, only 17.1% of individuals with a long (>=9 hours) unrefreshing main sleep period at W1 reported it again at W2. However, 56.7% of them were still reporting hypersomnolence symptoms at W2 just not an extended unrefreshing sleep.

Conclusions: Hypersomnolence symptoms are common in the general population and chronic for nearly half of the affected individuals. Interestingly, for a part of these individuals, we observed a change in the symptomatic expression of the hypersomnolence. This suggests that symptoms may evolve over time thus the importance of a detailed exploration of hypersomnolence symptoms.

446. Longitudinal Survey of Idiopathic Hypersomnolence Disorders in the General Population

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Introduction: Idiopathic Hypersomnia is a primary sleep disorder characterized by a prolonged main sleep period of unknown etiology. It can be very debilitating, resulting in difficulty maintaining employment and performing daily tasks, as well as social isolation and loneliness. Data related to its prevalence, incidence and chronicity in the general population is nearly non-existent.

Methods: This longitudinal study was carried out in eight states in the U.S. A total of 12,218 subjects were interviewed by phone during the first wave (W1) and 10,930 at the second wave (W2) three years apart. The analyses included only the subjects who participated in the 2 waves (N=10,930). Hypersomnolence was assessed according to DSM-5 criteria.

Results: At W1, 3.7% of the sample met the DSM-5 criteria for Hypersomnolence Disorder. Of these, 48.6% had Hypersomnolence Disorder with Mental Disorder and 53.4% had Hypersomnolence Disorder with a Medical Condition. Only 0.8% of the sample had an Hypersomnolence Disorder not associated with other disorders/conditions. More precisely, 0.45% had an Idiopathic Hypersomnolence Disorder associated with a prolonged sleep period (>=9 hrs) and 0.35% an Idiopathic Hypersomnolence Disorder with a normal sleep duration. At W2, 4.0% met the criteria for Hypersomnolence Disorder: 25.9% had Hypersomnolence Disorder with Mental Disorder and 44.2% had Hypersomnolence Disorder with a Medical Condition. Idiopathic Hypersomnolence Disorder was found in 1.2%: 0.58% was characterized with a prolonged sleep period and 0.62 an Idiopathic Hypersomnolence Disorder with a normal sleep duration. Chronicity of hypersomnolence disorder was 52.3%. The incidence of the Hypersomnolence Disorder was 0.3% per year.

Conclusions: Idiopathic Hypersomnolence Disorders are uncommon in the general population. It is also a poorly documented disorder for which there are large gaps in knowledge are present.

447. Clinically Relevant Effects of Solriamfetol on Excessive Daytime Sleepiness: A Post-Hoc Analysis of the Magnitude of Change in a Clinical Trial of Adults with Narcolepsy

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Introduction: Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, is approved in the US and EU to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy (approved dose range: 75-150 mg/d) or obstructive sleep apnea (OSA; approved dose range: 37.5-150 mg/d). The aim of the current analysis was to evaluate the effects of solriamfetol on measures of functioning and work productivity in a subgroup of participants with narcolepsy in a long-term open-label extension (OLE) study.

Methods: Participants with EDS associated with narcolepsy or OSA who completed previous solriamfetol studies were eligible. The long-term OLE study included a 2-week titration phase followed by a maintenance phase of ≤50 weeks (stable doses of 75, 150, or 300 mg). Assessments included the Functional Outcomes of Sleep Questionnaire short version (FOSQ-10) and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP; the specific health problem was either "narcolepsy" or "OSA"). Mean (standard deviation; SD) changes from baseline were summarized. Safety was also assessed. Data are reported for the subgroup of participants with narcolepsy.

Results: The safety population included 226 participants with narcolepsy. Increases (improvements) in mean FOSQ-10 total score from baseline (mean change [SD]: 3.7 [3.2]) were sustained for the duration of treatment with solriamfetol. On the WPAI:SHP, mean % reduction (improvement) from baseline was -26.7% for % activity impairment outside of work, -29.5% for % impairment while working (presenteeism), and -29.5% for % overall work impairment due to the problem ("narcolepsy"). Common adverse events (AEs; ≥5%) included headache, nausea, anxiety, nasopharyngitis, decreased appetite, insomnia, and dry mouth; 6 participants (2.7%) had ≥1 serious AE.

Conclusions: Solriamfetol demonstrated sustained improvements over approximately 1 year in measures of functioning and work productivity in participants with narcolepsy. The majority of AEs were mild to moderate in severity.

448. Kleine-Levin Syndrome is Associated with Trank1 Gene Variants in Conjunction with Birth Difficulties

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Kleine-Levin Syndrome (KLS) is a rare disorder characterized by severe episodic hypersomnia, with cognitive impairment, and behavioral disturbances such as apathy or disinhibition. Pathophysiology is unknown, although imaging studies indicate decreased activity in hypothalamic/thalamic areas and associative cortical areas during episodes. Familial occurrence is increased, and risk is associated with reports of a difficult birth. We conducted a worldwide case-control genome wide association study in 673 KLS cases collected over 14 years, and ethnically matched 15,341 control individuals. We found a strong genome-wide significant association (OR=1.48 at rs150168018, $p=8.6x10^{-9}$) with 24 single nucleotide polymorphisms (SNPs) encompassing a 35kb region located in the 5' region of *TRANK1* gene (tetratricopeptide repeat and ankyrin repeat-containing protein), a loci that was previously found to be associated with bipolar disorder and schizophrenia. Strikingly, KLS cases with *TRANK1* had statistically increased reports of a difficult birth. As perinatal outcomes have dramatically improved over the last 40 years, we further stratified our sample by birth years and found that recent cases had a significantly reduced *TRANK1* association. These findings were confirmed in an independent replication cohort of 171 new patients where polygenic risk scores constructed on the discovery cohort strongly replicated ($r^2=0.15$; $p<2.0x10^{-22}$ at p=0.5 threshold) and the *TRANK1* association was also found to be dependent on reports of birth difficulties (OR=1.54, p=0.01 versus OR=1.12, p=0.4). Pathway analyses revealed that rhythmic behavior pathway genes were significantly associated (adj. p=0.02) with KLS. Our results demonstrate links between KLS, behavioral rhythmicity, and bipolar disorder, and indicates that the TRANK1 polymorphisms in conjunction with reported birth difficulties predispose to KLS.

449. Sleep Disordered Breathing in Intracerebral Hemorrhage Survivors in Japan: A Meta-Analysis & Systematic Review

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Purpose: To evaluate the prevalence and association of sleep disordered breathing (SDB) in intracerebral hemorrhage (ICH) survivors in Japan.

Methods: A literature search was performed using Pubmed, Scopus, CINAHL and Clinicaltrials.gov through April 1, 2020 utilizing search terms related to intracerebral hemorrhage, hemorrhagic stroke, sleep apnea, sleep disordered breathing and Japan. Additional sources were found through forward and backward tracking of citations. Studies with apnea-hypopnea index (AHI) in ICH patients from

Japan were included. Studies from where this information was not available or deducible were excluded. The AHI was extracted from each study. Weighted averages were obtained using and random-effects model (RE) with 95% confidence intervals in accordance to SDB severity by AHI ≥: 5, 10, 15, 20, 30 and 40. Subgroup analysis were conducted using RE for: Location of testing; Stroke period (acute; subacute) during time of testing; Sleep study location; Prospective vs retrospective study.

Results: Two publications met inclusion criteria. The prevalence of SDB in ICH was found to be as follows for RE AHI: >5 91% (95% CI: 84-95); >15 in 56% (39-72); >30 in 22% (11-39); Mean AHI was 20.79 (95% CI: 14.04-27.55). Subgroup analysis for AHI >15 [65 (95% CI: 55-74); 48 [(95% CI: 40-55) p-value: 0.007] and AHI>30 30 (95% CI: 22-40); 15 (95% CI: 11-22) p-value: 0.005] showed: Patients from studies that were prospective had a higher AHI than retrospective; Patients in the medical unit had a higher AHI than those in a rehabilitation unit; Acute stroke period had a higher AHI than the subacute period. Subgroup analysis for AHI >5 or mean AHI was not statistically significant. Severe SDB (AHI >30) compared to non-severe or absence of SDB, was found to be higher in patients with the following: Dysarthria (90% vs 62% p-value: 0.006); Dysphagia (76% vs 51% p-value: 0.025); Dysarthria and dysphagia (76% vs 47% p-value: 0.008). Increased mean waist circumference [86 (84-92) vs 84 (78-88) p-value: 0.019] and mean BMI [23.8 (21.1-26.8) vs 21.5 (19.4-25) p-value: 0.046)] were also associated with severe SDB.

Conclusion: SDB in ICH survivors is higher in the acute period of stroke compared to subacute. This may be attributed to the pathogenesis of ICH, transience or high morbidity and mortality. Oropharyngeal motor impairment and obesity may be associated with SDB in ICH survivors in Japan.

450. Cholinergic Innervation of Genioglossus Motoneurons in the Context of Sleep Apnea

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Background: During Obstructive Sleep Apnea (OSA), excessive loss of tone of upper airway dilator muscles leads to airway collapse. Negative pressure or hypercapnia causes repeated arousals, resulting in sleep fragmentation. If left untreated, OSA can lead to serious health complications. One mechanism for excessive loss of tone of upper airway dilator muscles may involve cholinergic inhibition of motoneurons innervating these muscles. We focus on cholinergic pre-motor mechanisms modulating the genioglossus (GG) muscle, the most robust upper airway dilator muscle relevant for OSA.

Objective: The purpose of this study is to **(i)** identify the sources of cholinergic innervation to GG motoneurons in the hypoglossal nucleus (NuXII), and **(ii)** determine whether modulation of these cholinergic systems impact GG muscle activity during sleep.

Methods: In 6 ChAT-L10 reporter mice, we used conventional retrograde tracing to identify neurons projecting to NuXII, and confirmed the proportion of cholinergic neurons with immunohistochemistry for choline acetyltransferase. We then used conditional retrograde tracing to determine monosynaptic input to NuXII motoneurons, and confirmed the retrograde results with conditional anterograde tracing. To chemogenetically modulate identified cholinergic systems to NuXII in ChAT-ires-cre mice, we transfected these systems with activating or inhibiting receptors, using AAV8-hsyn-DIO-hM3Dq-mCherry and AAV10-hsyn-FLEX-hGlyR-a2-mCherry, respectively. We instrumented these mice for EEG, GG and neck EMG. We then recorded these mice in a plethysmograph under a repeated CO_2 arousal paradigm to mimic OSA while modulating transfected neurons using CNO (for hM3Dq) or IVM (for hGlyR) versus control.

Results: Cholinergic neurons projecting to NuXII are located in the parahypoglossal region (PH) and the upper cervical cord (UC). UC cholinergic neurons project to the center of NuXII with large terminal boutons, whereas PH cholinergic cells project to the periphery of NuXII with smaller terminal boutons, suggesting that cholinergic UC and PH populations are distinct. We found that chemogenetic activation of cholinergic UC neurons increased tonic GG activity during NREM sleep, prior to and after the onset of CO_2; conversely, inhibiting UC cholinergic neurons decreased tonic GG activity. This same pattern was not observed following chemogenetic modulation of PH cholinergic neurons.

Conclusions: Cholinergic neurons in the upper cervical and parahypoglossal regions represent anatomically and functionally distinct systems, with the former system modulating tonic GG activity during sleep. The differences between these systems may be exploited to selectively ameliorate excessive loss of upper airway dilator muscle tone during sleep in patients with OSA.

451. African-Americans Exhibit Lower Sleep Efficiency and CSF Alzheimer Biomarker Levels Than Non-Hispanic Whites

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Importance: Sleep and circadian function affect cerebrospinal fluid (CSF) Alzheimer disease (AD) biomarker levels. AD is more prevalent among African-Americans (AA) compared to Non-Hispanic whites (NHW), but there are limited data regarding effect of race on AD biomarkers, sleep/circadian function, and their interaction.

Objective: We examined the effect of race (AA vs NHW) on CSF AD biomarker levels, sleep and circadian function, and any relationship between sleep/circadian function and biomarkers. Design/Setting: Cross-sectional analysis of a clinical research cohort recruited from the St. Louis MO region, who underwent lumbar puncture for CSF biomarker measurement following an overnight sleep study and sleep/circadian assessment by actigraphy. Participants: Cognitively-normal participants (n=121) age 35-65 years, of whom 58 (48%) reported AA race and 62 (51%) reported NHW race. Obstructive sleep apnea (OSA) was present in 49 (40%) of participants. Main Outcome and measure: CSF AD

biomarker levels including Aβ40, Aβ42, and tau were measured by the automated Lumipulse platform. Sleep efficiency and circadian variables were assessed by wrist actigraphy.

Results: CSF Aβ40, Aβ42, and tau were lower in the AA compared to NHW group, a difference which was not accounted for by OSA diagnosis or age. Sleep efficiency was worse in the AA group compared to NHW group. Additionally, we found that people who had preclinical AD (amyloid-positive-as defined by tau/Aβ42 > 0.541) had worse sleep efficiency. We found that high circadian fragmentation was positively correlated with tau/Aβ42 and AD pathology.

Conclusion and Relevance: Race is an important variable that affects CSF AD biomarker levels as well as sleep/circadian function. We confirm, in this younger cohort, that preclinical AD is associated with worse sleep efficiency. Future research on the relationship of sleep/circadian function and AD biomarkers and pathophysiology should incorporate race as a key covariate.

Traumatic Brain Injury

246. Diffusion Tensor Magnetic Resonance Imaging of Hypothalamus in Traumatic Brain Injury Warfighters with Sleep Dysfunction

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Objective/Background: Traumatic brain injury (TBI) is the signature injury in U.S. military service members affecting over 20% of deployed combatants (Caldwell 2019). Over half of TBI victims experience sleep disorders (Castriotta 2007) to include insomnia and obstructive sleep apnea (OSA) - yet mechanisms remain unclear. We hypothesized that the hypothalamus, a critical regulator of sleep and respiratory function (Kuwaki 2010), may play a role in sleep dysfunction after TBI and that altered hypothalamic microstructure would be detectable with magnetic resonance imaging (MRI) via diffusion tensor imaging (DTI) in chronic TBI patients with sleep dysfunction.

Methods: We performed a retrospective cross-sectional study of 283 warfighters with mild, moderate, or severe TBI (Glasgow coma scale of 15-13, 12-9, or 8-3 on presentation, respectively) enrolled from the National Intrepid Center of Excellence and compared to a control group of 61 participants. Data gathered for the TBI group included age, body mass index (BMI), and diffeomorphic calculations of hypothalamus DTI scalar values (fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD)) (Pauli 2018) and in-lab overnight polysomnography (PSG). A type 1 error cutoff of $p < 0.05$ was used. Comparisons were made with the Student's T or nonparametric equivalent. Linear models were generated as described.

Results: We found that there was significant sleep dysfunction amongst the TBI group with an incidence of OSA of 60%. There was no difference in mean DTI measures between TBI and control (FA TBI 0.221 +/- 0.0234 vs control 0.222 +/- 0.0215, MD TBI $1.09*10^{-9}$ +/- $8.89*10^{-11}$ vs control $1.08*10^{-9}$ +/- $7.43*10^{-11}$, AD TBI $1.33*10^{-9}$ +/- $9.25*10^{-11}$ vs control $1.32*10^{-9}$ +/- $7.64*10^{-11}$, RD TBI $9.75*10^{-10}$ +/- $8.88*10^{-11}$ vs control $9.64*10^{-10}$ +/- $7.52*10^{-11}$). No DTI measure was predictive of PSG-derived outcomes such as apnea hypopnea index after controlling for age and BMI.

Conclusions: Diffeomorphic DTI quantification of the hypothalamus was not sensitive enough to distinguish mild to moderate TBI patients from controls. Furthermore, hypothalamic DTI scalars did not correlate with measures of sleep dysfunction. Limitations in resolution and signal to noise ratio likely explain our lack of findings. Use of sleep-related anatomy with more axon tracts may improve sensitivity. Additional studies to assess the pathologic basis of TBI sleep disorders are needed.

247. Age and Sex Moderate Effects of ABCC8 and TRPM4 Genetic Variability on Traumatic Intracerebral Hemorrhage Progression

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Introduction: Research suggests a key role of the Sur1-Trpm4 cation channel in traumatic brain injury (TBI) edema and hemorrhage progression. A large phase-2 trial of Sur1-Trpm4 inhibition in TBI is ongoing. Genetic variation may influence the differential extent and response of this secondary injury in patients. We previously reported single nucleotide polymorphisms (SNPs) in ABCC8 (Sur1) and TRPM4 associated with TBI hemorrhage progression. Age and sex may also affect progression, and can influence gene expression/regulation. We hypothesized that age and sex moderate effects of ABCC8 and TRPM4 SNPs on hemorrhage progression and progession extent after TBI.

Methods: DNA was extracted from 398 severe TBI patients. 25 previously identified ABCC8 and TRPM4 SNPs associated with 6h, 24h, and 120h hemorrhage progression on computed tomography were sequentially tested for interaction with age (centered at 16y), and sex. Binary and quantitative effects were evaluated. Multivariable models also controlled for GCS, admission hemorrhage volume, craniectomy before progression, thrombocytopenia and coagulation parameters.

Results: 12 SNPs (8 in ABCC8 and 4 in TRPM4) interacted with age to affect hemorrhage progression/extent, surviving Benjamini-Yekutieli adjustment for multiplicity ($p<0.0102$): rs2237982, rs2283261, rs1799857, rs8192695, rs2074311, rs717110, rs1799859, rs4148640, rs1477363, rs10410857, rs909010, rs3760666. Four of the ABCC8 SNPs, and one TRPM4 SNP, were cortex- and hippocampus-specific expression quantitative trait loci. At 16y, variant ABCC8 SNP rs2237982 was associated with an OR of 3.84 for 24h progression; this decreased by ~5.5% for every one-year increase in age ($p=0.001$). Conversely, ABCC8 homozygous variant rs757110

decreased hemorrhage progression at 6h (β=-12.8) and 24h (β=-13.3) at 16y, but these benefit decreased by 1.01mL ($p<0.001$) and 0.84mL ($p<0.001$), respectively, for each one-year increase in age. TRPM4 Homozygous variant rs1477363 quantitatively increased 24-hour hemorrhage progression at age=16y (β = 22.9), this decreased by 0.95mL with each additional year of age ($p<0.002$). Rs1477363 was also associated with quantitative hemorrhage progression in a sex dependent manner: while homozygous variants decreased 24-hour progression by -12.5 mL in males, it was associated with a large increase of 28.4 mL in females ($p_{interaction}<0.002$).

Conclusion: Almost 50% of ABCC8 and TRPM4 SNPs previously associated with TBI hemorrhage progression/extent, had age and/or sex dependent effects. Studies in biological models should evaluate functional implications and pathophysiology. If validated, this may directly inform trial design and analysis for Sur1-Trpm4 antagonists in TBI, and ultimately guide precision-medicine based risk-stratification and management.

248. Low-Field, Point-of-Care Magnetic Resonance Imaging of Subdural Hematoma

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Background and Aims: Recent advances in MRI technology have led to the development of a low-field (64 mT), point-of-care (POC) MRI device that allows for image acquisition at the bedside. The appearance of subdural hematoma (SDH) on POC MRI has not yet been described.

Methods: We studied four male patients (ages 65-90) presenting with a radiographic diagnosis of SDH. One patient presented with bilateral SDH, two patients presented with bilateral SDH and underwent left-sided SDH evacuation, and one patient presented with left-sided SDH and underwent left-sided evacuation. T1-weighted (T1W), T2-weighted (T2W), and fluid-attenuated inversion recovery (FLAIR) fast-spin-echo POC exams were obtained on all patients. POC MRI exams were analyzed by three independent raters using a standardized qualitative evaluation for subdural collection appearance, location, and morphology and a quantitative evaluation for SDH maximum thickness and midline shift (MLS). The three evacuated subdural spaces were evaluated for postoperative changes. Appearance of subdural collections were determined by majority consensus.

Results: POC exams were obtained at approximately six days (n=1), one month (n=1), and two months (n=2) since the initial time of incident. Average SDH maximum thickness and MLS measurements on POC exams ranged from 1.1-2.9 cm (median 1.4 cm) and 0.0-6.3 mm (median 0.2 mm), respectively. SDH collections were classified as chronic (n=1) and acute-on-chronic (n=3) based on conventional imaging. T1W POC exams demonstrated one chronic SDH collection as a mixed iso-hypointensity, two acute-on-chronic collections appeared as mixed iso-hypointensities, and one acute-on-chronic collection appeared as a homogeneous isointensity. T2W and FLAIR POC exams demonstrated one chronic SDH collection as hyperintense, two acute-on-chronic collections as mixed hyperintensities, and one acute-on-chronic collection as a homogenous hyperintensity. Pneumocephalus appeared as signal fallout at the site of SDH evacuation on one T1W, two T2W, and two FLAIR exams. Residual blood products were detected and appeared at the site of SDH evacuation as mixed iso-hypointensities on two T1W exams, mixed hyperintensities on two T2W exams, and mixed hyperintensities on two FLAIR exams.

Conclusion: These preliminary data detail the appearance of SDH and its postoperative evacuation changes on low-field, POC MRI. Further work is needed to detail the serial changes that accompany SDH progression and its surgical intervention.

249. Investigating the Role of the Claustrum in Consciousness Recovery Following Severe Brain Injury

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Traumatic brain injury (TBI) is one of the leading causes of death and disability globally, with enormous economic consequences. Approximately 69 million individuals sustain a TBI annually. Patients who have suffered TBIs may lead to loss of consciousness and this project aims to evaluate the role the insula plays in regaining consciousness. Previous research has shown that the claustrum may play a pivotal role in consciousness and we hypothesized that an increase in claustrum metabolic activity will be linked to clinical improvement. Twenty-four patients were prospectively recruited at WCM/NYP and classified into minimally conscious or vegetative state based on the JFK Coma Recovery Scale - Revised (CRS-R). MRI and [^{18}F]-FDG PET scans were acquired and contrasted to CRS-R scores. PET scans were reoriented, resliced and co-registered using PMOD software and the standardized uptake value (SUV) extracted (i.e., metabolic activity). Claustrum ROIs were defined following neuroanatomical references from the individual structural MRI, and data from baseline to follow-up were compared. We report here the pool of patients that showed significant improvement on the CRS-R score based on an arbitrary cutoff threshold (i.e., >3). These patients showed an increase in the mean claustrum SUV from baseline to the follow-up visit. Moreover, mean claustrum SUV signal differences correlates

with improvement of individual behavioral scores. This preliminary result supports the hypothesis that activity within the claustrum is linked to consciousness recovery in patients with severe disorders of consciousness. Further large longitudinal studies are required to assess the role of the claustrum.

250. Lack of Efficacy of Stem Cells in the Treatment of Chemosensory Dysfunction

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Background: Experimental evaluations utilizing mice have demonstrated that mesenchymal stem cells have been intranasally administered extending though the cribriform plate (Danielyan 2009). The use of stem cells intranasally through cribriform plate as a potential treatment for olfactory deficit has not previously been reported on.

Methods: The patient observed in this study is a 61 year old right handed male who had a traumatic brain injury. One month after the trauma he realized he lost his sense of smell and taste. Six months after initial presentation patient underwent fluoroscopic guidance for stem cell allograph placement. During the procedure 50 mg of placental stem cells were placed on each olfactory epithelium. The patient had no improvement in chemosensory function six months after placement.

Results: Prior stem cell Treatment: Chemosensory testing: olfaction: alcohol sniff test:1(anosmia). Retronasal smell index: 1(anosmia) Odor Memory Test: 1/12 (anosmia) Sniff magnitude test: 1.16(anosmia) Gustatory testing: Facial nerve function study: 26 on the right and 24 on the left. Taste quadrant testing: Right to left abnormality with decrease to sucrose and quinine. Front to back decrease in quinine Taste Testing: Hypogeusia to Sucrose, Urea, Phenylthiocarbamide, Ageusia to Hydrochloric acid, Normogeusia to NaCl. Post Stem Cell Treatment: Chemosensory testing: Olfaction: alcohol sniff test:1 (anosmia). Retronasal smell index: 1(anosmia). Odor Memory Test: 2/12 (anosmia) Sniff magnitude test: 1.08(anosmia) Gustatory testing: Facial nerve function study: 18 on the right and 16 on the left. Taste quadrant testing: No right to left difference. No front to back difference. Taste weak to hydrochloride acid. Taste Testing: Ageusia to Sucrose, Phenylthiocarbamide, Hydrochloric acid, Hypogeusia to Sodium chloride, Agnosia to urea.

Conclusion: Despite the negative results in the above treatment, theoretical justification for the use of stem cells in the treatment of olfactory deficits of a neural origin supports this approach. Furthermore, a greater response should be occurring in olfactory epithelium, where a normal state olfactory neural replication is a continuous process (Cheuk,2007). A more formalized trial of the use of mesenchymal stem cells at the olfactory epithelium or extending into the olfactory bulb is warranted.

251. Poor Sleep after Mild Traumatic Brain Injury is Associated with Increased Inflammation in Warfighters

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Introduction: Mild traumatic brain injury (mTBI) and sleep dysfunction are independently associated with persistent inflammation. Acutely after mTBI, pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), are elevated for days to months before declining (SunY, et al. Elevated levels of inflammation-related cytokines. FrontNeurol. 2019). In some patients, especially those with multiple and/or penetrating head injuries, chronic activation of microglia can last for years and has been associated with impaired functional recovery and mental health disorders (WitcherKG, et al. Priming the inflammatory pump. TrendsNeurosci. 2015.). IL-6, interleukin-10 (IL-10), and TNFα elevation have been associated with sleep dysfunction--a common sequela (>50%) of TBI--in a two-way relationship as both causes and effects (TappZM, et al. Sleep Disruption Exacerbates and Prolongs Inflammatory. JNeurotrauma. 2020). We hypothesize that inflammation triggered by mTBI is elevated in those who also have sleep dysfunction and that inflammatory cascades involving IL-6 and TNFα may serve as an important link between mTBI and sleep dysfunction.

Methods: In a retrospective cross-sectional convenience cohort of warfighters (n=137 mTBI, 44 controls), the Pittsburgh Sleep Quality Index (PSQI) was compared with exosome and plasma IL-6, IL-10, and TNFα (mean=10 years from last mTBI). Single Molecule Array achieved protein quantification. Tests were performed using a type I error of $p<0.05$. Linear models controlled for age, sex, and body mass index.

Results: In the mTBI cohort, poor sleepers (PSQI>=10) had significantly elevated IL-6 pg/mL [standard deviation] (exosomes: 0.47 [0.63] vs 1.01 [1.54], p=0.04, d=0.44; plasma: 5.00 [13.3] vs 6.88 [13.5], p=0.03, d=0.14) compared to good sleepers (PSQI<10) and PSQI directly correlated with IL-6 (exosomes: R=0.21, p=0.02; βstd=0.30, p=0.01) and TNFα (exosomes: R=0.22, p=0.01; βstd=0.12, p=0.02). These findings were not observed in controls. In the mTBI cohort, good sleepers had significantly greater IL-10 levels (exosomes: 1.71 [8.18] vs 0.30 [0.54], p=0.02). However, these findings were reversed after removing outliers, which yielded that IL-10 was significantly elevated in mTBI poor sleepers (exosome: 0.12 [0.12] vs 0.16 [0.12], p=0.02). These findings were not observed in controls.

Conclusion: Warfighters who report poor sleep have significantly elevated inflammatory and varying levels of anti-inflammatory interleukins after chronic mTBI. Poor sleep may contribute to prolonged activation and elevation of

cytokines after mTBI. These findings may have therapeutic implications.

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252. Longitudinal Changes in Cerebral Blood Flow after Traumatic Brain Injury

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Background: Patients who sustain a mild TBI often show no abnormalities on conventional magnetic resonance imaging (MRI). Arterial spin labeling (ASL) allows for non-invasive quantitative imaging of cerebral blood flow (CBF) and may be useful in the evaluation of microvascular function after TBI.

Methods: We enrolled 38 hospitalized adult subjects with mild TBI (median GCS 15; IQR 14-15) who underwent 3T MRI scanning in the acute period after injury (mean 20 days post-injury), 11 of whom were also scanned in the chronic stage (6-12 months post-injury). Six additional mild TBI patients were scanned only in the chronic stage. Age- and gender-matched healthy volunteers (n=18) were also enrolled as a control group. Whole-brain CBF maps were derived using a 3D pseudo-continuous ASL (3DpCASL) technique. CBF z-score maps were generated relative to healthy controls to identify clusters of hypo- and hyperperfusion at the individual subject level. Tissue volumetric changes were assessed using tensor-based morphometry. Clinical outcomes, including Glasgow Outcome Scale-Extended (GOSE) score, were assessed at 6 months post-injury and used to classify TBI patients with and without full recovery. CBF, cluster count, and total cluster volume were compared between groups using t-tests. Imaging measures were also assessed in the subset of patients with longitudinal data using a within-subject statistical design.

Results: Global CBF did not significantly differ between TBI subjects and controls. TBI patients in the acute and chronic phase exhibited greater number and volume of both hypo- and hyperperfused clusters compared to controls. In patients with longitudinal data, CBF increased significantly within hypoperfused clusters and decreased significantly within hyperperfused clusters from the acute to chronic phase. Volumetric changes were modest and suggested a trend toward atrophy in hypoperfused clusters by 6 months post-injury. Global CBF in the acute phase was significantly higher in subjects with full recovery (GOSE=8) at 6 months post-injury compared to those with incomplete recovery (GOSE<8). Total cluster volume of both hypo- and hyperperfusion in the acute phase was also significantly lower in subjects who made a full recovery.

Conclusions: Our findings suggest that CBF is altered in a multifocal fashion after mild TBI, with evidence of normalization in both hypo- and hyperperfused regions by 6 months post-injury. Our findings also suggest a link between CBF in the acute phase and subsequent clinical recovery. ASL may be useful in characterizing the natural history of microvascular dysfunction after TBI.

253. Post-Traumatic Exercise-Induced Pseudo-Cerebrospinal Fluid Rhinorrhea

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Introduction: While rhinorrhea of cerebrospinal fluid (CSF) is a well described complication of head injury, rhinorrhea without actual CSF leakage following such an event has rarely been described (Cusimano, *J Neurosurg* 1994). Post-traumatic pseudo-CSF rhinorrhea occurring exclusively while exercising, has not heretofore been reported.

Case Report: This 61-year old right-handed male was knocked-down, hitting his head on the pavement, with loss of consciousness for 5 minutes. A CT scan at the time revealed bifrontal hemorrhages. For two months afterwards, he suffered from low-pitched tinnitus and blurred vision, all of which resolved within four months of the trauma. He had also lost his sense of smell and taste, what persisted, associated with a decrease in appetite and a 5-pound weight loss. Additionally, he developed severe headaches, which came on gradually in occipital regions bilaterally and would occur daily for the first two months. Since the trauma, while exercising even for short time periods, he would develop bilateral clear nasal drainage. This would occur, for instance, after lifting weights, bicycling or running for very short distances. This did not exist prior to the trauma and has not improved for 4 years since then. Treatment with ipratropium bromide nasal spray markedly reduced the rhinorrhea.

Results: Chemosensory testing revealed anosmia and ageusia. A CT scan done five months prior to presentation revealed sinusitis, treated with antibiotics, but nasal discharge persisted, and there was no change in smell or taste. Nasal discharge analysis was negative for glucose. The radionuclide cisternogram was normal. Fiberoptic endoscopy was also normal.

Discussion: This most likely represents pseudo-CSF rhinorrhea since the CSF cisternogram was normal and it only occurred with exercise, as opposed to spontaneously, with positional change or with Valsava maneuver. The mechanism for such remains unclear. It has been suggested this is due to dysautonomia, an imbalance between parasympathetic and sympathetic discharge, secondary to an injury to parasympathetic fibers. That this is pseudo-CSF rhinorrhea as opposed to actual CSF rhinorrhea is reinforced by the fact that symptoms were markedly reduced after treatment with ipratropium bromide nasal spray, an anticholinergic agent,

and its use has been described for pseudo-CSF rhinorrhea (Hilinski, *Otology & Neurotology* 2001).

Conclusion: The importance of recognition of exercise-dependent pseudo-CSF rhinorrhea to prevent invasive surgery to correct a condition that can be medically managed, suggests that this be explored in any patients who present with similar symptoms.

254. Paroxysmal Sympathetic Hyperactivity Syndrome in Severe Traumatic Brain Injury: Patient Characteristics, Utilization of Sedation, Analgesia and Anesthetic Intravenous Infusion Medications and Patient Outcome

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Introduction: Paroxysmal sympathetic hyperactivity syndrome (PSHS) is often seen after severe TBI (sTBI). Studies discussing specific sedation, analgesia and anesthetic intravenous infusion medications (SAAIM) use for PSHS are lacking. *We aim to compare the characteristics, utilization of SAAIM and outcomes of patients who develop PSHS versus those who do not among patients with sTBI. We also aim to explore if PSHS is an independent predictor of outcome among* patients with sTBI.

Methodology: This is a single-center retrospective cohort study. Adult patients admitted from January 1, 2016 to September 30, 2017 with acute sTBI under the NSICU service were included in the study. Patients were grouped according to those with a PSHS diagnosis (PSHS) versus those who do not (non-PSHS). The primary outcome was intensive care unit (ICU) length of stay (LOS). Linear regression was done to determine the independent predictors of ICU LOS, hospital LOS (HLOS) and ventilator days (VD).

Results: Sixty-three patients were included. PSHS was diagnosed in 24%(15) patients with sTBI. Most of the patients with PSHS were 48±23 years old, male(13,87%), caucasian(8,53%) with an admission GCS of 5±2. The demographic, clinical, and radiographic characteristics are comparable between the PSHS versus Non-PSHS cohorts except for higher proportion of illicit substance use (7,47% vs10,21%,p=0.049), higher proportion of occurrence of intracranial hypertension (7,47%vs5,10%, p=0.002), and longer duration of intracranial pressure (ICP) monitoring (15±6vs7±4days, p=0.011). The most commonly used SAAIM overall for sTBI patients were propofol(39,62%). The PSHS cohort utilized a higher number of SAAIM (3±2vs2±1, p=0.047) while fentanyl(10,67%vs18,38%, p=0.047) and morphine(4,27%vs3,6%, p=0.028) infusions were utilized at higher proportion than the non-PSHS cohort. The PSHS cohort had longer ICU LOS (11.67± 11.08vs5.81±5.18, p=0.006), HLOS (25.20±42.62vs9.77± 9.31, p=0.021), and VD (8.63±8.73vs4.87±4.68, p=0.040). Linear regression analysis revealed that the duration of ICP monitor, not PSHS, is an independent predictor of ICU LOS for sTBI patients.

Conclusion: We have shown that patients with PSHS have higher proportion of illegal substance use, occurrence of intracranial hypertension, longer duration of ICP monitoring and larger utilization of SAAIM. These patients also were found to have significantly longer ICU LOS and HLOS as well as VD. The duration of ICP monitor is an independent predictor of ICU LOS for patients with sTBI. Data from this study can be utilized for further prospective studies on PSHS management and outcomes.

255. Diffusion Tensor Imaging Correlates of Concussion Related Cognitive Impairment

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Introduction: Concussion is defined as an alteration in mental status induced by a head trauma that may or may not involve loss of consciousness. Some of the clinical features that have been described as sequelae of mild traumatic brain injury (TBI)/concussion are cognitive impairment, behavior abnormalities, and mood disorders. The Montreal Cognitive Assessment (MOCA) has been a promising tool with high sensitivity to screen for occult memory impairment in patients with mild TBI and post-concussion syndrome. Diffusion Tensor Imaging (DTI) is shown to reliably quantify the microstructural integrity of brain tissue, thereby serving as a valuable biomarker for TBI. Previous studies demonstrate that decreased fractional anisotropy (FA) and increased mean diffusivity (MD) are found in concussion, especially in the corpus callosum, amygdala, cerebellum, hippocampus, and thalamus. Our objective was to identify the findings in DTI that are associated with MOCA scores in patients with cognitive impairment post-concussion.

Methods: 53 subjects (19 females; the age of 51.39 ± 19.09) with a history of concussion due to various etiologies, including sports-related, car accidents, and falls, leading to varying degrees of cognitive decline and neuropsychologic symptoms, were included in this study. The subjects had a MOCA and DTI. We performed whole-brain atlas-based DTI segmentation through MRICloud software (168 regions) and obtained FA and MD values. We conducted a random forest-based recursive feature selection (RFE) with 10-fold cross-validation in the entire dataset for all the regions FA and MD values to compute the importance for each predictor and remove redundant predictors of MOCA scores. Then, the partial correlation adjusted for age was performed to identify the correlations between MOCA scores and DTI findings.

Results: MOCA scores were 23.56 ± 5.81. RFE showed that 57 DTI variables were found to be important predictors of MOCA scores and were included in the correlation analyses. Partial correlation analyses corrected for age showed a significant correlation with MOCA scores and limbic system structures: right amygdala MD (r=-0.70, p=5.02e-07), right inferior temporal gyrus MD (r=-0.70, p=2.49e-07), left

hippocampus MD (r=-0.60, p=0.0001), and right fornix FA (r=0.55, p=0.001).

Conclusion: Although limbic system structures are relatively protected from the direct impact of trauma, they were found to be the most significant predictors of cognition after concussion, similar to non-traumatic etiologies of cognitive impairment, such as Alzheimer's Disease and Multiple Sclerosis.

K-588. ABCC8 And TRPM4 Genetic Variability Is Associated With Intracerebral Hemorrhage Progression After Severe Traumatic Brain Injury

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Introduction: Intracerebral hemorrhage progression strongly prognosticates unfavorable outcome after traumatic brain injury (TBI). The Sur1-Trpm4 cation-channel is central to this process- possibly an extreme form of vasogenic edema and blood-brain-barrier breakdown. A phase-II trial of Sur1-Trpm4 inhibition in contusion-TBI is ongoing. Research suggests genetic variability influences hemorrhage progression. *ABCC8* (Sur1) and *TRPM4* genetic variability have previously been associated with TBI edema and/or outcome. Based on known pathophysiology and brain endothelial expression, we hypothesized that *ABCC8* and *TRPM4* single nucleotide polymorphisms (SNPs) predict TBI hemorrhage progression.

Methods: DNA was extracted from 398 severe-TBI patients. Exomic and non-exomic ABCC8 and TRPM4 SNPs were genotyped (multiplex). Hemorrhage progression at 6, 24, and 120h was quantified. Since craniectomy affects hemorrhage progression, primary analyses excluded these patients. Secondary analyses included all-comers. Multivariable regression analyses evaluated SNP associations with hemorrhage progression.

Results: 49.3% patients had hemorrhage progression within 120h. 40 SNPs were analyzed. 16 *ABCC8* SNPs were associated with hemorrhage progression (p<0.05); five survived multiple comparison corrections. Homozygous variant rs2283261 (OR 4.77, *p=0.00097*), rs2237982 (OR 3.80, *p=0.00046*), and rs3819521 (OR 3.92, *p=0.009*) markedly increased odds of progression within 120h. Rs2283261 was associated with hyperacute (6h, OR 4.15, *p=0.007*) and acute (24h, OR 4.06, *p=0.002*) progression. Rs2237982(OR 3.35, *p=0.001*) and rs8192695 (OR 4.95, p=0.004) were associated with acute progression. Rs916827 (β=5.92, p=0.009) quantitatively increased 120h progression. Three (rs2283261, rs2237982, rs3819521) have also been associated with TBI edema/outcome, cluster downstream, flank exons encoding the receptor site/juxtapose the channel pore, and are brain expression quantitative trait loci (eQTL). Four TRPM4 SNPs (all brain-eQTLs) were significant. Homozygous wild-type rs3760666 (OR 2.23, *p=0.009*), rs1477363 (OR 2.32, *p=0.008*), rs10410857 (OR 2.76, *p=0.001*), and rs909010 (OR 3.14, *p=0.00033*) were associated with acute progression. Rs1477363 (OR 2.34, *p=0.007*), rs10410857 (OR 2.65, *p=0.002*), and rs909010 (OR 2.90, *p=0.00056*) increased odds of 120h progression. Rs909010 was associated with 6h progression (OR 2.76, *p=0.007*). In all-comers, all SNPs were associated with progression (*p<0.05)*, with rs10410857 and rs909010 surviving the multiplicity threshold.

Conclusions: Five variant ABCC8 SNPs increased odds of hemorrhage progression with large effect sizes; three have previously been associated with TBI edema and/or outcome, increasing plausibility of biological significance. WildtypeTRPM4 SNPs increased odds of hemorrhage progression. True functional consequences remain currently undetermined. If validated, this may have important implications for risk stratification, patient selection, and precision medicine based targeted therapy.

K-592. Selective Inhibitory Circuit Dysfunction In The Orbitofrontal Cortex Is Associated With Cognitive Inflexibility After Traumatic Brain Injury

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Traumatic brain injury (TBI) is a leading cause of neurologic disability and the most common associated cognitive deficits affect prefrontal cortex (PFC)-dependent functions such as: attention, working memory, social behavior, and mental flexibility. Despite this prevalence, little is known about the pathophysiology that develops in frontal cortical microcircuits after TBI. In our mouse model of frontal lobe contusion that recapitulates aberrant mental flexibility as measured by deficits in rule reversal learning, we investigated if deficits in inhibitory neuronal firing and synaptic transmission are associated with cognitive inflexibility after TBI. Patch clamp recordings were performed in layer V pyramidal and inhibitory neurons two months after injury in the orbitofrontal cortex (OFC). The principal output neurons, the pyramidal neurons, showed minimal change in function with only a minor reduction in the action potential threshold in TBI compared to sham cohorts; and the fast-spiking interneurons had identical action potential (AP) and passive membrane properties in both groups. In contrast, the non-fast spiking inhibitory neurons, presumably somatostatin(SOM)-expressing, exhibited a striking vulnerability to injury with a wider AP half width, reduced falling AP slope, and an increase in the adaptation index leading to reduced excitability and fewer action potentials produced at depolarizing current steps after TBI. Furthermore, analysis of SOM-mediated inhibitory currents in layer V pyramidal neurons evoked with specific optogenetic stimulation of somatostatin interneurons identified a reduction in synaptic response after TBI. Given that SOM+ inhibitory neurons play a crucial role in dampening of excessive activity in cortical circuits, dissecting why these inhibitory neurons are selectively vulnerable to injury may be a key component in restoring cognitive function after TBI.

ANA 2020 Author Index

ANA 2020 Keyword Index

N

P

R

S

T

V