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LETTER TO THE EDITOR

Acute and late neurological complications of COVID19: the quest for evidence

Weixi Xiong,[1,2,3] Patrick Kwan,[4,5] Dong Zhou,[1] Alessandra Del Felice,[6] John S. Duncan[2,3] and Josemir W. Sander[2,3,7]

1 Department of Neurology, West China Hospital of Sichuan University, Chengdu, 610041, Sichuan, China
2 NIHR University College London Hospitals Biomedical Research Centre, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK
3 Chalfont Centre for Epilepsy, Chalfont St Peter SL9 0RJ, UK
4 Department of Neuroscience, Central Clinical School, Monash University, Alfred Hospital, Melbourne, Parkville, Victoria, Australia
5 Departments of Medicine and Neurology, Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia
6 Department of Neuroscience, NEUROMOVE Rehab Lab, and Padova Neuroscience Center, University of Padova, Italy
7 Stichting Epilepsie Instellingen Nederland - (SEIN), Heemstede, The Netherlands

Correspondence to: Prof Ley Sander
UCL Queen Square Institute of Neurology
Queen Square London, WC1N 3BG, UK
E-mail: l.sander@ucl.ac.uk

There is inevitable uncertainty when a new disease strikes and understanding the full spectrum of COVID-19 neurological complications is no exception. Neurologists in endemic areas are diligently working to understand the impact of COVID-19 on the nervous system. To date, more than 100 articles have been published on the neurological aspects of COVID-19 but there are insufficient high-quality cohort studies or case series to elucidate the full picture. We, therefore, read with interest, in *Brain*, the case series of potential acute neurological complications of COVID-19 in individuals seen at a tertiary neurological referral centre in the UK during the peak of the recent outbreak (Paterson *et al.*, 2020). Forty-three clinical cases were described in detail including history, examination and extensive investigations. The authors are to be commended for their care and diligence. This case series adds to our knowledge about the potential spectrum of neurological features but, as noted by the authors, leaves many questions unanswered. Table 1 lists selected reports of neurological interest and complications.

First, there is uncertainty about the actual incidence, prevalence and scale of neurological complications as the denominator is not known at this stage (Herman *et al.*, 2020). Of note, proportionally more cases of neurological complications of SARS-CoV-2 have been reported, than with two other corona viruses, SARS-CoV and MERS-CoV, at similar stages of the disease trajectory. This may be due to the scale of COVID-19, compared to the numbers of SARS and MERS cases. One multicentre Chinese study suggested that the incidence of COVID-19 neurological complications could be $<5\%$ (Xiong *et al.*, 2020). A national reporting database from the UK described 114 cases with confirmed neurological or neuropsychiatric complications (Varatharaj *et al.*, 2020). With nearly 300 000 cases of COVID-19 in the UK this is likely to be a significant underestimate, because of reporting bias. Realistic epidemiological estimation will only be possible with well-designed national or international studies that take into account differences across populations and healthcare settings. This is challenging given there are confounders such as genetic predisposition, viral evolution, and local preventative measures.

Second, the causality of neurological impairments needs to be carefully evaluated (Ellul *et al.*, 2020). Evidence of a direct viral insult to the CNS is lacking. Most CSF examinations failed to detect the virus (Destras *et al.*, 2020; Moriguchi *et al.*, 2020). No post-mortem examination to date has found direct evidence of the virus in the brain (Bian and the Covid-Pathology Team., 2020; Solomon *et al.*, 2020), concurring with the findings in the recent case series in *Brain* (Paterson *et al.*, 2020). A much higher incidence of ischaemic strokes was, however, noted among patients with COVID-19 compared to those with influenza (Merkler *et al.*, 2020). Studies are needed to ascertain if there are

Table 1 Cohort or case series reports ($n \geqslant 4$) in PubMed with well-described methodology and neurological details in COVID-19 (including articles involving drug intervention issues)

	Location	Age group	Study design	Cases with neurological complications or investigated	Key findings
Xiong *et al.*, 2020	China	All ages	Multicentre retrospective observational	32 cases in 917 individuals	Clinical findings
Varatharaj *et al.*, 2020	UK	Adult	Multicentre retrospective/ prospective case reports	125 (114 COVID-19 positive)	Clinical findings
Kandemirli *et al.*, 2020	France	Adult	Multicentre retrospective observational	12 cases in 749 individuals	MRI and CSF findings
Toscano *et al.*, 2020	Italy	Unknown	Multicentre retrospective observational	5 cases in up to 1200 individuals	GBS associated with COVID-19
Romero-Sánchez *et al.*, 2020	Spain	Unknown	Duo-centre retrospective observational	483 cases in 841 individuals	Clinical findings
Merkler *et al.*, 2020	USA	Adult	Duo-centre retrospective observational	31 cases in 1916 individuals	COVID-19 related Stroke
Mao *et al.*, 2020	China	Unknown	Retrospective observational	78 cases in 214 individuals	Clinical findings
Destras *et al.*, 2020	France	All ages	Retrospective observational	2 cases in 578 individuals	CSF findings
Cabezudo-García *et al.*, 2020	Spain	Unknown	Cross-sectional observational	21 cases in 1537 individuals (9 in 511 tested positive)	COVID-19 incidence in people with epilepsy
Kremer *et al.*, 2020	France	All ages	Multicentre case series	37 cases in 190 individuals	MRI, EEG and CSF findings
Paterson *et al.*, 2020	UK	Adult	Case series	43 (29 COVID-19 positive)	Clinical findings
Helms *et al.*, 2020	France	Adult	Case series	58	Clinical findings in intensive care unit
Galanopoulou *et al.*, 2020	USA	Adult	Retrospective case series	28 (22 COVID-19 positive)	EEG findings
Solomon *et al.*, 2020	USA	Adult	Case series	14	Brain histopathological findings
Coolen *et al.*, 2020	Belgium	Adult	Prospective case series	19 amongst 62 individuals	Post-mortem MRI findings
Beyrouti *et al.*, 2020	UK	Adult	Case series	6	Stroke associated with COVID-19
Oxley *et al.*, 2020	USA	Adult	Case series	5	Stroke associated with COVID-19
Abdel-Mannan *et al.*, 2020	UK	Children	Case series	4	Clinical findings

GBS = Guillain-Barré syndrome.

unique COVID-19 related factors that increase stroke risk compared to other viral infections. In the longer term, it is not certain whether there will be an increase of immune-mediated neurological diseases such as acute demyelinating encephalomyelitis (ADEM)-like and Guillain-Barré syndrome (Toscano *et al.*, 2020), consequent to COVID-19, akin to the increased incidence of narcolepsy seen after the H1N1 pandemic (Partinen *et al.*, 2014). Close long-term follow-up of well-defined cohorts of subjects who recovered from COVID-19 are required to clarify this.

Third, the clinical spectrum in this case series is in accord with reports from China, Spain and the UK (Mao *et al.*, 2020; Romero-Sánchez *et al.*, 2020; Varatharaj *et al.*, 2020; Xiong *et al.*, 2020). Impairment of consciousness and stroke were the most common features in all series, but ADEM-like illness was not previously reported, which may reflect a local ascertainment bias. It is not possible to compare rates of peripheral neurological disorders between the different reports due to differences in the definitions used. The current case series suggests that seizures were rare, with or without a prior history of epilepsy (Lu *et al.*, 2020).

The full spectrum of neurological complications is worthy of further investigation, by larger well-designed studies. There are also likely differences in the clinical spectrum of neurological impairments according to age, such as a predominance of cerebrovascular complications in older subjects (Varatharaj *et al.*, 2020; Xiong *et al.*, 2020).

Neurological complications of children with COVID-19 are less well established. Early reports suggested children were spared from COVID-19 and, if infected, developed less severe illness, but increasing numbers of paediatric cases developing severe systemic inflammatory response requiring hospitalization are being reported. A recent report described four children presenting with a distinct neurological syndrome associated with lesions in the splenium of the corpus callosum evident on neuroimaging (Abdel-Mannan *et al.*, 2020). Further work is needed to determine whether a unique or more prominent pattern of neurological complications exists in different age groups.

Fourth, the knowledge of COVID-19-related sequelae will contribute to the design of appropriate rehabilitation pathways. The need for pulmonary rehabilitation is well established (Liu *et al.*, 2020), while the physical consequences of COVID-19 are less well described. Admission to an intensive care unit with prolonged immobilization, pronation cycles and mechanical ventilation with curarization, may trigger neurological complications. Prolonged physical inactivity due to admission to less intensive wards or home confinement may play a role in cognitive and motor dysfunction, especially in the elderly (Carda *et al.*, 2020). At present, there are around 90 registered ongoing studies (https://clinicalstudies.info.nih.gov; https://clinicaltrials.gov; https://www.clinicaltrialsregister.eu) on rehabilitation in COVID-19, with tentative protocols based on the partial knowledge of medium and long-term sequelae.

Future studies need to have an adequate sample size, be prospective, have an estimate of the denominator, and use consistent terms and definitions, include detailed history, including existing comorbidities, and have standardized examinations and investigations.

To date, there are no reports of specific subacute or chronic complications post-COVID-19 infection, but some are predictable such as cognitive impairment in survivors of mechanical ventilation or encephalopathy. We need to remain vigilant to post-COVID-19 neurological symptoms, with well-designed follow-up studies and surveillance, which may be achieved by linkage to national health databases.

To accelerate knowledge building on COVID-19, we call for an international, collaborative, and open-access registry to follow prospectively large numbers of individuals who recover from COVID-19 (https://neuroscienze.unipd.it/public/files/neuromove/Projects2/coper.pdf). Most COVID-19 reports are from China, Europe and the USA and little is known in terms of neurological complications in other regions where the pandemic is now raging such as Africa, India and Latin America. Data sharing and international collaboration are particularly important and beneficial, when considering the gaps in research capabilities in countries with limited resources.

There is strength in numbers and sustained effort is needed to understand and optimize treatment of the neurological sequelae of this disease that has changed the world since its onset in December 2019.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests in relation to this work.

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