



RESEARCH

Open Access



Brain perfusion changes in beta-thalassemia

Renzo Manara¹, Sara Ponticorvo^{2,3}, Marcella Contieri⁶, Antonietta Canna^{2,4}, Andrea Gerardo Russo^{2,5}, Maria Cristina Fedele⁶, Maria Chiara Rocco⁷, Adriana Borriello⁸, Silvia Valeggia¹, Maria Pennisi⁶, Marianna De Angelis⁶, Domenico Roberti⁶, Mario Cirillo⁵, Francesco di Salle², Silverio Perrotta^{6*} , Fabrizio Esposito⁵ and Immacolata Tartaglione⁶ 

Abstract

Background Brain injury in hereditary hemoglobinopathies is commonly attributed to anemia-related relative hypoperfusion in terms of impaired oxygen blood supply. Supratentorial and infratentorial vascular watershed regions seem to be especially vulnerable, but data are very scarce.

Aims We investigated a large beta-thalassemia sample with arterial spin labeling in order to characterize regional perfusion changes and their correlation with phenotype and anemia severity.

Methods We performed a multicenter single-scanner cross-sectional 3T-MRI study analyzing non-invasively the brain perfusion in 54 transfusion-dependent thalassemia (TDT), 23 non-transfusion-dependent thalassemia (NTDT) patients and 56 Healthy Controls (HC). Age, hemoglobin levels, and cognitive functioning were recorded.

Results Both TDT and NTDT patients showed globally increased brain perfusion values compared to healthy controls, while no difference was found between patient subgroups. Using age and sex as covariates and scaling the perfusion maps for the global cerebral blood flow, beta-thalassemia patients showed relative hyperperfusion in supratentorial/infratentorial watershed regions. Perfusion changes correlated with hemoglobin levels ($p=0.013$) and were not observed in the less severely anemic patients (hemoglobin level >9.5 g/dL). In the hyperperfused regions, white matter density was significantly decreased ($p=0.0003$) in both patient subgroups vs. HC. In NTDT, white matter density changes correlated inversely with full-scale Intelligence Quotient ($p=0.007$) while in TDT no correlation was found.

Conclusion Relative hyperperfusion of watershed territories represents a hemodynamic hallmark of beta-thalassemia anemia challenging previous hypotheses of brain injury in hereditary anemias. A careful management of anemia severity might be crucial for preventing structural white matter changes and subsequent long-term cognitive impairment.

Keywords Brain, Perfusion, Thalassemia, Hemoglobin, Transfusions

[†]Renzo Manara and Sara Ponticorvo equally contributed and should be considered first coauthors.

*Correspondence:
Silverio Perrotta
silverio.perrotta@unicampania.it

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Introduction

Beta-thalassemia is a rare congenital anemia caused by defective production in the beta-globin chain of hemoglobin. The clinical phenotype is rather heterogeneous. The most severe forms require regular blood transfusions from the first years of life to survive until adulthood (Transfusion Dependent Thalassemia, TDT), while less severe patients receive transfusions occasionally, e.g., during infections or pregnancy (Non Transfusion Dependent Thalassemia, NTDT). In regularly transfused patients, the target is to keep pre-transfusion hemoglobin level at 9.0–9.5 g/dL, to balance the risks of hypertransfusion (e.g., excessive iron overload) and chronic anemia [1]. In general, the management of disease- or treatment-related complications is complex and multisystem deterioration usually occurs in spite of careful laboratory and clinical monitoring. Besides heart, liver and endocrine glands, the brain is another known target of disease complications and cognitive functioning has been shown repeatedly to be impaired, especially among adult TDT patients [1]. However, the precise pathogenesis of brain involvement still remains unclear. Iron overload does not seem to directly affect the neural tissue as iron does not seem to cross the blood-brain barrier in spite of very high serum levels [2–4]. White matter microvascular impairment is also questionable, at least among patients treated according to the current guidelines [5, 6]. Intracranial vasculature (arteries and venous sinuses) does not appear to be significantly involved as increased rate or evolution of intracranial stenosis, venous thrombosis, and aneurysms were not confirmed in recent literature [5, 7]. Recently, a regionally specific vulnerability of the white matter was shown in a large sample of anemias, including beta-thalassemia [8]. In particular, decreased white matter volume and microstructural integrity were found in the watershed areas, i.e. the white matter regions that are in between two main cerebral artery territories [8, 9], suggesting an increased regional perfusion vulnerability of the brain. For these reasons, we performed a multicenter single-scanner cross-sectional MRI study analyzing non-invasively in beta-thalassemia patients and healthy controls the brain perfusion changes occurring in relation with clinical phenotype, age, hemoglobin levels, cognitive functioning and parenchymal lesions. The aims of this study were to (i) confirm and characterize perfusion changes in beta-thalassemia according to phenotype, demographic data and laboratory findings and (ii) correlate regional perfusion changes to parenchymal abnormalities and cognitive functioning impairment.

Materials and methods

Subjects

Patients with diagnosis of beta-thalassemia and age > 16 years were recruited from 4 referral centers for

beta-thalassemia. Patients were considered with TDT if on a regular transfusion regimen; those who were not regularly transfused and had not received any transfusion during the last 48 weeks before the enrolment were enrolled as NTDT patients. Contraindications to MRI, history of neurologic disease, head trauma or neurosurgery were exclusion criteria. A clinical chart review allowed the collection of clinical and laboratory data related to the disease history and severity; laboratory parameters were collected as mean of last year's values. In TDT patients, hemoglobin value at MRI was calculated according to post-transfusion hemoglobin level and the rate of hemoglobin decrease per day using a well-established formula applied for transfusion planning in beta-thalassemia patients. All data were acquired between June 2016 and June 2017. We recruited 77 beta thalassemia patients (54 TDT and 23 NTDT patients) and 56 healthy controls. The latter group was volunteers aged > 16 years mostly recruited among patients' relatives and entourage with a negative history for neurological, hematological, neoplastic or systemic disease, including anemia.

Patients and healthy subjects also participated in our previous multimodal MRI studies [1, 3, 5, 6]. The study was approved by the Ethic Committee (161/2015), and all subjects, both patients and controls, signed an Informed Consent before data collection.

MRI data evaluation

All study participants underwent brain MRI on the same 3T scanner (MAGNETOM Skyra, Siemens, Erlangen Germany) with a 20-channel head coil.

Cerebral Perfusion weighted maps (PWI) were obtained from brain images acquired using a 3D Pulsed Arterial Spin Labeling (PASL) sequence. Imaging parameters and data analysis methodology can be found in our auditory cortex perfusion study [10].

In order to account for the intrinsic inter-subject variability related to both physiological and technical aspects of ASL acquisition, PWI images were considered both before and after value normalization by the global cerebral blood flow (obtaining a relative cerebral flow, rCBF). A global value was calculated for each subject the mean PWI across all the voxels in the brain was calculated and used as a normalization factor. For the voxel-wise analysis, a general linear model (GLM) full factorial design (as implemented in SPM12 package <https://www.fil.ion.ucl.ac.uk/spm/>) was used (in both analyses) with one between-subject factor (group) of three levels (HC, TDT, NTDT) and two covariates (age and sex). T-maps were thresholded at $p < 0.001$ voxel-level and only clusters at $p < 0.05$ family-wise error corrected at the cluster level were considered significant.

Table 1 Patients’s demographics and clinical characteristics

	TDT (n=54)	NTDT (n=23)	All Patients (n=77)	Controls (n=56)
Mean age, years	36.4±9.2	30.3±11.5	34.6±10.5	33.9±10.8
Females, n (%)	34 (62.9)	13 (56%)	47 (61.0)	36 (64.3)
Splenectomized, n (%)	35 (64.8)	9 (39%)	44 (57.1)	0
Hb*(g/dL), mean±SD	9.2±0.5	9.3±0.9	9.3±0.8	NA
Hb at MRI (g/dL), mean±SD	9.6±1.1	9.3±0.9	9.5±1	NA
Ferritin (ng/mL), mean±SD	877.0±684.4	364.1±290.8	736.2±641.7	NA
LIC (mg/gdw), mean±SD	4.3±3.0	6.7±5.4	4.9±3.7	NA
Iron Chelation Therapy				
DFO, n (%)	14 (25.9)	2 (8.7)	16 (20.8)	0
DFP, n (%)	4 (7.4)	0	5 (6.5)	0
DFX, n (%)	35 (64.8)	4 (17.4)	38 (49.3)	0

*mean Hb in TDT refers to pre transfusional values; LIC: liver iron concentration; DFO: Deferoxamine; DFP: Deferiprone; DFX: Deferasirox

All patients (TDT and NTDT) were additionally subdivided based on hemoglobin levels (9.5 g/dL cut-off level) and the two subgroups were further separately compared to HC in terms of whole brain brain perfusion.

Finally, mean white matter (WM) density in the cluster of significant perfusion difference was also extracted and compared between groups. Particularly, the whole brain maps of WM density were obtained from tissue

segmentation using SPM12, and the mean across all the voxels in the cluster mask was extracted for each subject.

Cognitive functioning assessment

Study subjects underwent a pool of psychometric tests included in the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) [1]. For this analysis Full-Scale Intelligence Quotient (FSIQ) and WAIS main domain scores were considered .

Statistical analysis

Comparisons between groups were performed using the T test, the Mann-Whitney U test and the Chi-square test (or the Fisher Exact test when required) for respectively normally distributed, ordinal and qualitative non-ordinal variables. The linear correlation between two variables was tested using Spearman’s correlation. Statistical significance was set at $p < 0.05$. Finally, an analysis of covariance (ANCOVA) was used to assess the linear dependence of the mean rCBF values in the significant clusters and hemoglobin values. The effect of group (HC, TDT and NTDT) on WM density in the cluster of hyperperfusion was compared with a 1-ANOVA and two-sample post-hoc t-tests.

Results

Patients’ and controls’ main clinical characteristics are summarized in Table 1.

Beta-thalassemia patients showed globally increased brain perfusion values compared to HC (Fig-1a); the finding was confirmed also considering patients subgroups (TDT and NTDT; Fig-1b-c), while no difference was found between TDT and NTDT subgroups (data not shown).

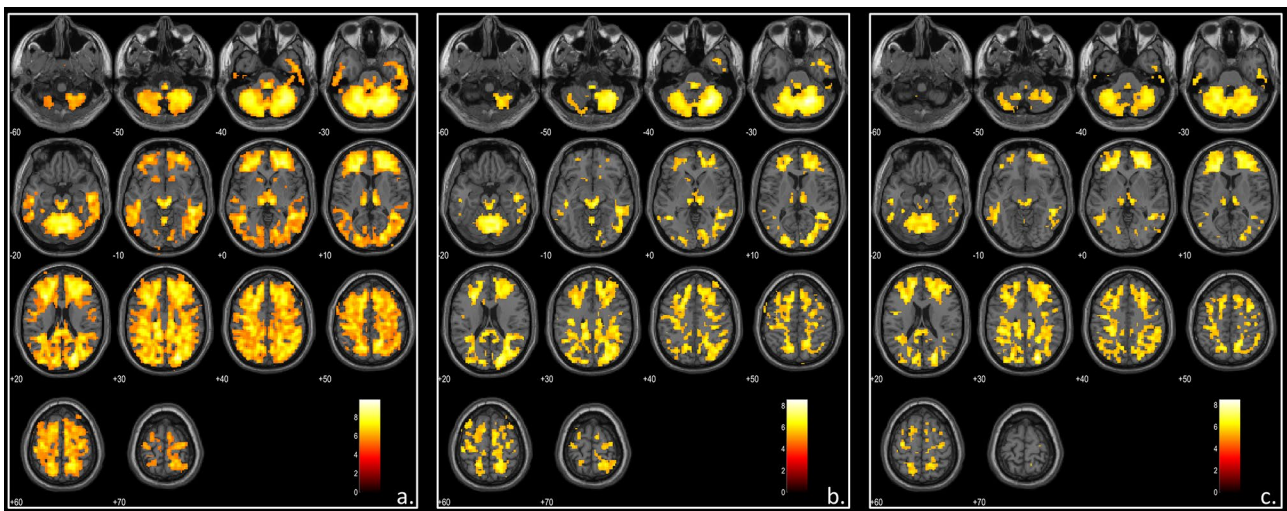


Fig. 1 Analysis of brain perfusion without correcting for global cerebral blood flow. T-maps showing significantly globally increased perfusion (colored areas) compared to healthy controls in thalassemia patients (a) transfusion dependent thalassemia patients (b) and non-transfusion dependent thalassemia patients (c)

Compared to healthy controls, using age and sex as covariates and scaling the perfusion maps for the global CBF, beta-thalassemia patients showed:

1. Several almost symmetric clusters of relative hyperperfusion in the white matter of the centrum semiovale bilaterally, located in the watershed regions between the vascular territories of the main cerebral arteries (namely the anterior, middle and posterior cerebral arteries) (Fig-2a).
2. Bilateral clusters of relative hyperperfusion in the cerebellar white matter corresponding to the cerebellar watershed regions (Fig-2a).

Similar hyperperfusion clusters were obtained comparing HC with patient subgroups (Fig-2b-c); clusters were more evident in the HC-vs-TDT comparison, most likely because of sample size. No significant perfusion differences emerged comparing TDT vs. NTDT or splenectomized vs. non-splenectomized patients.

In patients, both cerebral and cerebellar hyperperfusion clusters correlated with hemoglobin levels ($p=0.013$) even when subdividing patients according to phenotype severity (Fig-3a-b).

Subdividing patients according to anemia severity (hemoglobin level $<$ or $>$ 9.5 g/dL) the hyperperfusion clusters persisted exclusively in the subgroup with lower hemoglobin levels (Fig-3c-d).

No correlation was found between perfusion values and ferritin, liver iron concentration or chelation treatment.

White matter density in the cluster of perfusion alteration was significantly decreased ($p=0.0003$, $F(df=2)=8.83$) in both patients subgroups vs. HC (post-hoc t-test: HC vs. TDT $p=0.00047$; HC vs. NTDT

$p=0.0049$). No significant differences in white matter density were detected while subgrouping patients according to phenotype or anemia severity ($p>0.05$).

In NTDT, white matter density changes correlated inversely with FSIQ ($p=0.007$, $\rho=0.584$), while in TDT no correlation was found ($p=0.96$, $\rho=0.007$).

No correlation emerged between hyperperfusion values and full-scale intelligence quotient scores or main WAIS domains (PRI, PSI, VCI and WMI).

Discussion

The present MRI study investigated brain perfusion in a large sample of beta-thalassemia patients and healthy controls. While confirming the expected compensatory global increase of cerebral blood perfusion secondary to anemia severity (regardless of phenotype), the study also showed in beta thalassemia patients significantly increased relative perfusion in the cerebral and cerebellar watershed territories.

So far, brain tissue injury in anemias has been mostly ascribed to possible chronic impairment of oxygen and nutrient supply due to relative regional hypoperfusion. Watershed territories have been consistently considered at increased risk due to long perforating vessel high functional vulnerability. This hemodynamic regional vulnerability is well known in major vessel occlusions (e.g. in internal carotid artery occlusion with an inefficient circle of Willis compensation, in moyo-moya disease, etc.). Similarly, watershed territories have been considered at risk in severe anemia, whenever the increase in blood perfusion did not compensate for low hemoglobin levels [11]. Vascular-like lesions in these regions (mostly located in the centrum semiovale deep white matter [12, 13]) have been therefore considered as the hallmark

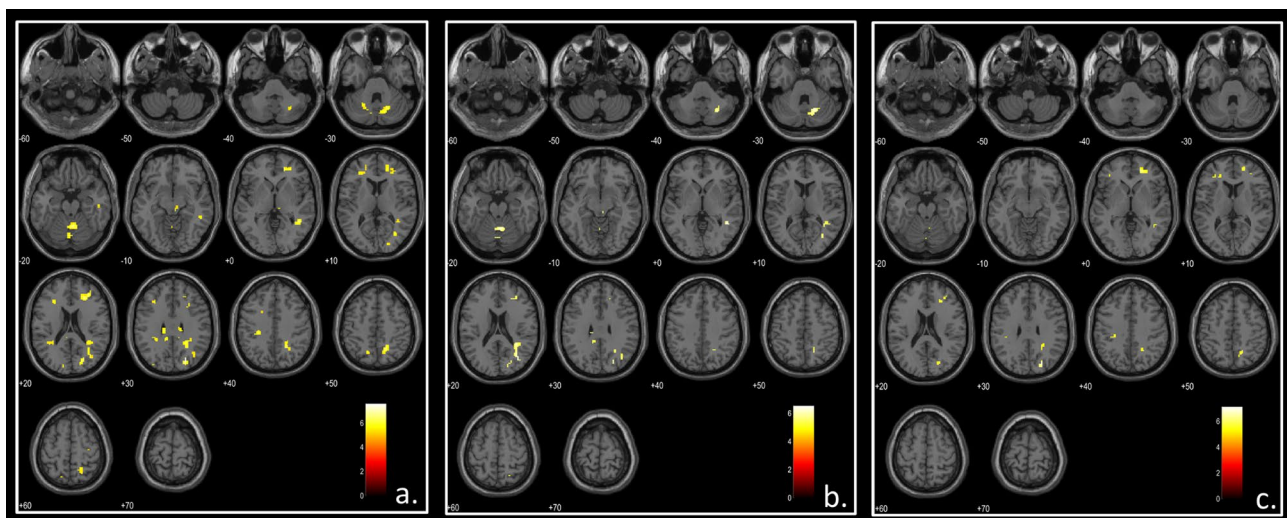


Fig. 2 Analysis of brain perfusion correcting for global cerebral blood flow. T-maps showing significantly increased perfusion (colored areas) compared to healthy controls in thalassemia patients (a) transfusion dependent thalassemia patients (b) and non-transfusion dependent thalassemia patients

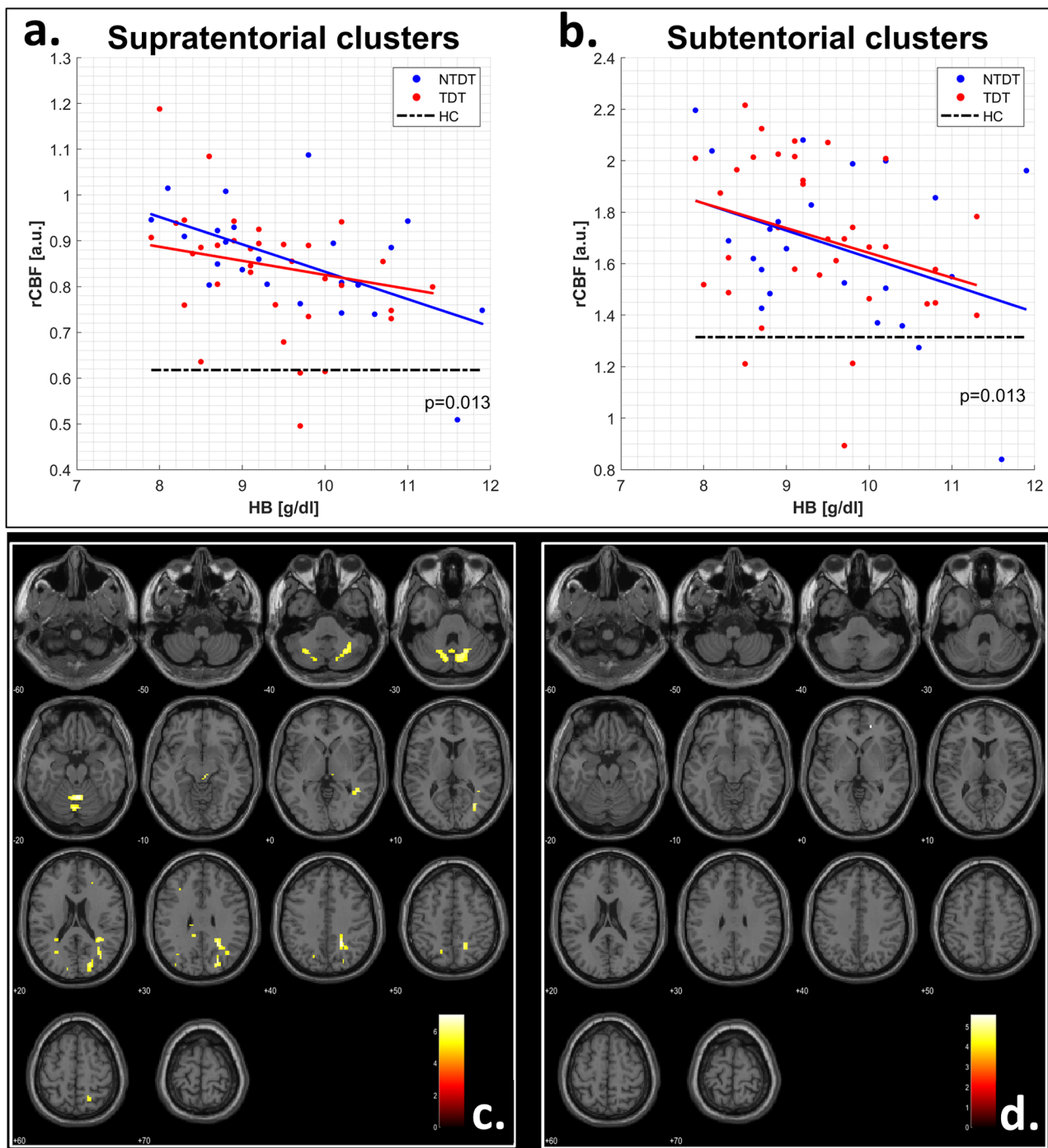


Fig. 3 (A and B) Scatter plots and fitted linear trends of the correlation between regional perfusion values and hemoglobin levels. Blue dots and lines represent non-transfusion thalassemia (NTDT) patients while red dots and lines represent transfusion thalassemia (TDT) patients. Black dashed lines represent mean perfusion values in the same clusters across all healthy controls (HC). (C and D) Analysis of brain perfusion separating thalassemia patients based on hemoglobin levels (Hb < 9.5 g/dL, panel C; Hb > 9.5 g/dL, panel D)

of anemia-related brain damage and several studies on other genetically determined hemoglobinopathies such as sickle cell disease have shown watershed silent infarcts in up to 40% of pediatric patients [13].

Recently, Choi and colleagues have shown decreased white matter volume and microstructural integrity in the watershed regions in a large sample of anemia patients (including beta-thalassemia subjects) [8, 9], supporting the hypothesis of an increased regional vulnerability

to hypoperfusion in conditions of anemia. Even though white matter volume changes were not confirmed in a whole brain voxel-based analysis on our beta-thalassemia population [14], this evidence was considered highly interesting and prompted further perfusion analyses on our study population. The analyses showed an unexpected finding in the watershed territories with relative hyperperfusion in comparison with healthy subjects instead of hypoperfusion, thus reversing, at least in beta-thalassemia, the pathogenetic hypothesis of white matter injury. Indeed, white matter is known to be vulnerable to both hypoperfusion and hyperperfusion [15]. Although the latter is less known, increased cerebral blood perfusion might be associated with blood–brain barrier breakdown, abnormal cerebrovascular reserve, increased blood flow velocities and subsequent parenchymal injury. Interestingly, restricting the analysis to the areas of relative hyperperfusion, decreased white matter volume was found also in our study population compared to healthy controls, suggesting not only that volume changes might be subtle, so that they emerge only with focused analysis, but also supporting a strict relationship between regional hemodynamics and white matter changes, that challenges in beta-thalassemia the pathogenic role of chronic impairment of oxygen and nutrients supply.

The fact that relative hyperperfusion in the watershed territories correlates to the severity of anemia might explain the white matter volume and connectivity decrease according to anemia severity [8, 9] as a consequence of enduring relative hyperperfusion instead of hypoperfusion. According to our study, the more the patient is anemic, the more perfused is his brain, the higher is the relative hyperperfusion in his supra and infratentorial watershed territories.

In addition, the linear regression analysis indicates that, in beta-thalassemia, perfusion values normalize with hemoglobin levels above 12 g/dL, i.e. at those ranges that are considered normal in the general population. This fact implicitly confirms that hemoglobin levels are the major determinant for perfusion changes in both TDT and NTDT patients, thus minimizing the role of other possible disease-related factors. However, keeping hemoglobin above 12 g/dL is not acceptable for the excess iron loading while levels above 9.5 g/dL seem to be sufficient to keep brain hyperperfusion changes at a non-significant level compared to healthy controls. Therefore, our findings reinforce the strict adoption of the recommendations from the Thalassemia International Federation setting the pretransfusion hemoglobin level at 9.5 g/dL, as the desirable target for protecting the brain while minimizing the iron poisoning of all the other organs (the brain appears to be protected from iron overload as shown in a previous study on this issue) [3].

Two main study findings appear controversial. Firstly, differently from relative hyperperfusion values, white matter volume reduction was independent from hemoglobin levels. Indeed, our analysis considered the hemoglobin level at the MRI scan, while volume changes likely result from a cumulative injury during hemoglobin level fluctuations in the patients' life. According to this explanation, patient management should aim at keeping hemoglobin persistently above those levels that are associated to watershed areas relative hyperperfusion.

Besides, white matter density changes were correlated with cognitive deficits only in NTDT patients who are known to be cognitively less affected than TDT. Possibly, with increasing disease severity, other factors such as a higher rate of hospitalization, transfusion related complications etc. might have a major impact in cognition overcoming the effect of structural white matter changes.

Limits

This is the first study investigating brain perfusion in a sufficiently large beta-thalassemia sample. We applied a non-invasive MRI technique, but there are some other techniques (e.g. contrast enhanced perfusion MRI, ^{15}O - H_2O positron emission tomography, multi-delay arterial spin labeling, etc.) that need to be applied to confirm and validate our findings.

Hemoglobin levels on the day of MRI were not available in healthy controls for ethical and cost reasons. As the sample was relatively large while the probability to have sudden asymptomatic abnormal levels of hemoglobin in asymptomatic subjects without history of anemia or polycythemia is rather low, we are confident that this aspect should not have had a significant impact on the study findings. Hypothesizing a high rate of low hemoglobin level in the healthy subgroup would imply that beta-thalassemia per se and not hemoglobin levels is the reason for a dramatic increased brain perfusion in patients. Hypothesizing a high rate of polycythemia in our control group is weird as the estimated prevalence of polycythemia in the general population is about 22 per 100,000 [16].

Our multicenter study included only Italian centers in order to centralize MRI examinations on a single scanner and minimize technical confounding factors. A multicenter study including other European and extra-European centers is required to validate our data in a multiracial and multi-environment setting.

Conclusions

Relative hyperperfusion of supratentorial and infratentorial watershed territories seems to represent a hemodynamic hallmark of beta-thalassemia anemia shedding a new light on the pathogenesis of brain injury in hereditary anemias. A careful management of anemia severity

might be crucial for preventing structural white matter changes and subsequent long term cognitive impairment.

Acknowledgements

We would like to thank prof. Alessandra Bertoldo for helpful suggestions, the authors and all the patients and healthy volunteers who participated in the study.

Author contributions

All authors (RM, SP, MC, AC, AGR, MCF, MCR, AB, SV, MP, MDA, DR, MC, FDS, SP, FE, IT) collected data, reviewed and approved the final manuscript. SP analyzed MRI images. RM and IT had full control of dataset during the study. RM, MC and IT drafted the manuscript. RM, FE, Silverio P and IT designed the study.

Funding

Study partially supported by VALERE project and "Giovani ricercatori" project.

Data availability

Data not shared to protect patients' privacy as still used for ongoing research, but available upon request to the corresponding author in anonymized files.

Declarations

Ethical approval and consent to participate

Study was approved by local IRB (161/15).

Consent for publication

All participants consented to the publication of study results.

Competing interests

The authors declare no conflict of interest.

Author details

¹Neuroradiology, Department of Neuroscience, University of Padua, Padua, Italy

²Dipartimento di Medicina e Chirurgia, Scuola Medica Salernitana, Università di Salerno, Fisciano, Italy

³Center for Magnetic Resonance Research (CMRR), Department of Radiology, University of Minnesota, 2021 6th St. SE, Minneapolis, MN 55455, USA

⁴Department of Radiology, Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, USA

⁵Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Napoli, Italy

⁶Dipartimento della Donna, del Bambino e di Chirurgia generale e specialistica, Università degli Studi della Campania "Luigi Vanvitelli", Via Luigi de Crecchio 4, Napoli 80138, Italy

⁷Pediatrics and Residency Program of Pediatrics, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Baronissi 84081, Italy

⁸Department of Precision Medicine, University of Campania "L. Vanvitelli", Via Luigi de Crecchio 7, Naples, Italy

Received: 4 December 2023 / Accepted: 19 April 2024

Published online: 21 May 2024

References

- Tartaglione I, Manara R, Caiazza M, Carafa PA, Caserta V, Ferrantino T, et al. Brain functional impairment in beta-thalassaemia: the cognitive profile in Italian neurologically asymptomatic adult patients in comparison to the reported literature. *Br J Haematol*. 2019;186:592–607.
- Cappellini MD, Farmakis D, Porter J, Taher A et al. Guidelines for the management of Transfusion Dependent Thalassemia (4th edition - version 2.0). Thalassemia International Federation. 2021.
- Manara R, Ponticorvo S, Tartaglione I, Femina G, Elefante A, Russo C, et al. Brain iron content in systemic iron overload: a beta-thalassemia quantitative MRI study. *Neuroimage Clin*. 2019;24:102058.
- Witzleben CL, Wyatt JP. The effect of long survival on the pathology of Thalassemia major. *J Pathol Bacteriol*. 1961;82:1–12.
- Tartaglione I, Russo C, Elefante A, Caiazza M, Casale M, Di Concilio R, et al. No evidence of increased cerebrovascular involvement in adult neurologically-asymptomatic β -Thalassaemia. A multicentre multimodal magnetic resonance study. *Br J Haematol*. 2019;185:733–42.
- Russo AG, Ponticorvo S, Tartaglione I, Caiazza M, Roberti D, Elefante A, et al. No increased cerebrovascular involvement in adult beta-thalassemia by advanced MRI analyses. *Blood Cells Mol Dis*. 2019;78:9–13.
- Manara R, Caiazza M, Di Concilio R, Ciancio A, De Michele E, Maietta C, et al. Asymptomatic intracranial aneurysms in beta-thalassemia: a three-year follow-up report. *Orphanet J Rare Dis*. 2020;15:21.
- Choi S, O'Neil SH, Joshi AA, Li J, Bush AM, Coates TD, et al. Anemia predicts lower white matter volume and cognitive performance in sickle and non-sickle cell anemia syndrome. *Am J Hematol*. 2019;94:1055–65.
- González-Zacarias C, Choi S, Vu C, Xu B, Shen J, Joshi AA, et al. Chronic anemia: the effects on the connectivity of white matter. *Front Neurol*. 2022;13:894742.
- Manara R, Ponticorvo S, Perrotta S, Barillari MR, Costa G, Brotto D, et al. Auditory cortex hypoperfusion: a metabolic hallmark in Beta thalassemia. *Orphanet J Rare Dis*. 2021;16:349.
- Dowling MM, Quinn CT, Plumb P, Rogers ZR, Rollins NK, Koral K et al. Acute silent cerebral ischemia and infarction during acute anemia in children with and without sickle cell disease [Internet]. *Blood*. 2012. pp. 3891–7. <https://doi.org/10.1182/blood-2012-01-406314>.
- Adams RJ. Stroke Prevention and Treatment in Sickle Cell Disease [Internet]. *Archives of Neurology*. 2001. <https://doi.org/10.1001/archneur.58.4.565>.
- Manara R, Talenti G, Rampazzo P, Ermani M, Montanaro M, Baracchini C et al. Longitudinal evaluation of cerebral white matter hyperintensities lesion volume in children with sickle cell disease. *Br J Haematol*. 2017. p. 485–7.
- Manara R, Canna A, Caiazza M, Ponticorvo S, Russo AG, Di Concilio R et al. White matter volume changes in adult beta-thalassemia: negligible and unrelated to anemia and cognitive performances. *Am J Hematol*. 2020. p. E142–4.
- Moore DF, Altarescu G, Barker WC, Patronas NJ, Herscovitch P, Schiffmann R. White matter lesions in fabry disease occur in prior selectively hypometabolic and hyperperfused brain regions. *Brain Res Bull*. 2003;62:231–40.
- Ma X, Vanasse G, Cartmel B, Wang Y, Selinger HA. Prevalence of polycythemia vera and essential thrombocythemia. *Am J Hematol*. 2008;83(5):359–62.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.