haematologica
Journal of the Ferrata Storti Foundation

Posterior cerebral circulation in children with sickle cell anemia: an uncharted territory

by Alvise Fattorello Salimbeni, Ludovica De Rosa, Alessia Volpato, Federica Viaro, Alessio Pieroni, Stefano Mozzetta, Francesco Favruzzo, Alessandra Pes, Matteo Zaccagnino, Giulia Reggiani, Maria Paola Boaro, Raffaella Colombatti, Renzo Manara, and Claudio Baracchini

Received: April 28, 2024.
Accepted: October 11, 2024.

Citation: Alvise Fattorello Salimbeni, Ludovica De Rosa, Alessia Volpato, Federica Viaro, Alessio Pieroni, Stefano Mozzetta, Francesco Favruzzo, Alessandra Pes, Matteo Zaccagnino, Giulia Reggiani, Maria Paola Boaro, Raffaella Colombatti, Renzo Manara, and Claudio Baracchini. Posterior cerebral circulation in children with sickle cell anemia: an uncharted territory. Haematologica. 2024 Oct 24. doi: 10.3324/haematol.2024.285773 [Epub ahead of print]

Posterior cerebral circulation in children with sickle cell anemia: an uncharted territory

Alvise Fattorello Salimbeni[1], Ludovica De Rosa[1], Alessia Volpato[1], Federica Viaro[1], Alessio Pieroni[1], Stefano Mozzetta[1], Francesco Favruzzo[1], Alessandra Pes[1], Matteo Zaccagnino[1], Giulia Reggiani[2], Maria Paola Boaro[2], Raffaella Colombatti[2], Renzo Manara[3], Claudio Baracchini[1]

[1]Stroke Unit and Neurosonology Laboratory, Azienda Ospedale-Università Padova, Padova, Italy.
[2]Pediatric Hematology Oncology Unit, Azienda Ospedale-Università Padova, Padova, Italy.
[3]Neuroradiology Unit, Azienda Ospedale-Università Padova, Padova, Italy.

Running Head: Posterior cerebral circulation in Sickle Cell Anemia

Corresponding author: Raffaella Colombatti, raffaella.colombatti@unipd.it

Data-sharing agreement: Data are available on request to the authors

Acknowledgments
This research was partially supported by a grant from the Fondazione Città della Speranza.

Funding Declaration
This research was partially supported by a grant from the Fondazione Città della Speranza.

Authors' contributions
RC, RM, CB designed the study. AFS, LDR, AV, FV, AP, SM, FF, AP, MZ collected neurosonologic and neuroradiologic data and performed the analysis. GR, MP collected patient demographics and clinical data. AFS, LDR and CB wrote the manuscript. All authors reviewed and approved the manuscript.

Conflict of interests:
RC received funding for participation in Advisory Boards/Consultancy from Vertex, Agios, Global Blood Therapeutics, Pfizer, Novonordisk, Forma Therapeutics, Novartis, Addmedica

Posterior cerebral circulation in children with sickle cell anemia: an uncharted territory

Alvise Fattorello Salimbeni[1], Ludovica De Rosa[1], Alessia Volpato[1], Federica Viaro[1], Alessio Pieroni[1], Stefano Mozzetta[1], Francesco Favruzzo[1], Alessandra Pes[1], Matteo Zaccagnino[1], Giulia Reggiani[2], Maria Paola Boaro[2], Raffaella Colombatti[2], Renzo Manara[3], Claudio Baracchini[1]

Affiliations

[1]Stroke Unit and Neurosonology Laboratory, Azienda Ospedale-Università di Padova, Padova, Italy.

[2] Pediatric Hematology Oncology Unit, Azienda Ospedale-Università di Padova, Padova, Italy.

[3]Neuroradiology Unit, Azienda Ospedale-Università di Padova, Padova, Italy.

Key Words: Sickle cell disease — transcranial ultrasound — magnetic resonance imaging — posterior circulation — intracranial stenosis — silent infarct

Sickle cell Anemia (SCA) is the most common hereditary hemoglobinopathy worldwide.[1] Neurological complications are a leading cause of mortality and disability in children with SCA.[2] The neurosonological screening protocol from the Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial has significantly improved long-term survival and disability.[3-5] However, silent cerebral infarcts (SCIs) with a prevalence of 39% by age 18 remain a major cause of cognitive dysfunction, including developmental failure, cognitive decline, and poor academic achievement, leading to social isolation.[6-7] Noteworthy, the STOP trial focused only on anterior brain circulation, excluding posterior circulation hemodynamics and silent ischemic lesions.

This study aimed to assess the parenchymal and vascular involvement of the posterior cerebral circulation and the role of transcranial ultrasound in detecting children with SCA at a higher risk of ischemic lesions in that territory.

In this cross-sectional observational study, we evaluated children affected by SCA (HbSS or HbSβ°), aged 2–18 years, attending the Veneto Region Pediatric SCD Reference Center of Padua University Hospital from March 1st 2005 to May 6th 2023. A clinical and hematologic assessment was completed every three months, or more frequently, if needed. Transcranial ultrasound was performed at steady state annually starting at 2 years of age, or more frequently according to the surveillance protocol.[3] A brain Magnetic Resonance Imaging/Magnetic Resonance Angiography (MRI/MRA) was performed every two years starting when sedation is no longer necessary - generally at 6 years of age – or in case of clinical and/or ultrasound indication. Demographics, clinical and treatment data of all patients were prospectively and systematically recorded in a SCA Database. The study was approved by the Research Ethics Committee of Padua University Hospital, and written informed consent was obtained by each caregiver.

Transcranial Doppler (TCD) and Transcranial Color-Coded Doppler (TCCD) were performed on every patient until 2016; thereafter, patients were assessed only using TCCD because no

differences were detected between results obtained with the two techniques.[8] The following vessels were evaluated: right and left terminal internal carotid artery (TICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA) and top of the basilar artery (BA) via a transtemporal approach; vertebral arteries (VA) and BA via a transforaminal approach. For each vessel, the highest value of the time averaged mean of the maximum velocities (TAMMV) was recorded. No angle correction was applied and ultrasound contrast agents were never administered. The STOP criteria were applied on MCA and TICA values as follows: Normal (TAMMV 70-169 cm/s in all vessels), Conditional (TAMMV 170–199 cm/s in at least one vessel), Abnormal (TAMMV >200 cm/s in at least one vessel), Low flow (TAMMV <70 cm/s in at least one vessel). Inadequate scans for any reason (poor scanning window, uncooperative patient, incomplete or equivocal scan) were classified as "Incomplete examination" and the patient was either re-assessed after a few days or sent to MRA.

The MRI/MRA study protocols were previously described.[7,9] In this analysis, the most recent MRI/MRA with a transcranial doppler performed within 12 months was considered.

After assessing their asymmetric distribution through the Shapiro-Wilk test, continuous variables were presented as median and interquartile range (IQ), while categorical data as number and percentage. Mann-Whitney U-test, Pearson chi-square test and Fisher exact test were employed as appropriate for statistical analysis. Results were considered significant with a p-value < 0.05. Statistical analyses were performed using Jamovi software.

One hundred-fifteen consecutive SCA (HbSS or HbSβ°) patients aged 2-18 years were evaluated; 87 were included in the analysis (Figure 1).

Among the study population, 75% of patients were on treatment at the time of TCD/TCCD: 63.2% were on Hydroxyurea (HU), while 5.7% were on chronic blood transfusion for recurrent vaso-occlusive crisis non responsive to HU (n.4) or previous Abnormal TCD (n.1) (Table 1). It is worth highlighting that no cerebrovascular events were reported previously nor during study period, while 50% of patients had suffered from acute chest syndrome and 12.5% from spleen sequestration. Neurological examination was normal in all.

Ultrasound findings were categorized according to the STOP trial protocol (Table 1): only one (1.1%) patient was categorized as Abnormal.

Cerebral ischemic lesions were detected in 25 (28.7%) patients (Table 2). All but one were located at the border-zone of vascular territories. Posterior border-zones were involved in 17 patients (19.5%), bilaterally in 8 (9.2%) (Supplementary Figures 1 and 2). Selective posterior border-zone involvement was observed in 3 (3.4%) children. Surprisingly, the posterior border-zone lesion burden was not inferior to the anterior one [median volume 264 cc (IQR 66-754) versus 60.5 cc (IQR 34.4-736), p 0.244]. A total of 125 intracranial stenoses were detected in 42 patients (48.3%). Posterior circulation stenoses were present in 8 children (9.2%): all of them involved the PCAs, bilaterally in 5 (5.7%). In most of these patients (6/8; 75%) the anterior circulation was also affected. Concerning posterior circulation ischemic lesions, a concomitant ipsilateral PCA stenosis was detected in 7/25 (28%). Interestingly, the presence of a PCA stenosis was associated with an ipsilateral ischemic lesion in the posterior border-zones in 7/13 cases (53.8%, $p < 0.0001$), while the detection of a MCA stenosis was not (5/29 MCA stenosis, no significant association with an ipsilateral lesion, 17.2%, $p = 0.62$).

As shown in Supplementary Table 1, despite a similar percentage of intracranial artery stenoses (52.9% vs 47.1%, p=0.788), the rate of posterior circulation stenoses was significantly higher in children with posterior border-zone lesions compared to children without lesions (4/17, 23.5% vs 4/70, 5.7%; p=0.042). Similarly, the rate of PCA stenosis

remained significantly higher when considering right and left PCA individually (8/34 overall PCAs in 17 patients with posterior lesions, 23.5% vs 6/140 PCAs in 70 patients without posterior lesions, 4%; p=0.00) in relation to its bilateral involvement (4 vs 1). Noteworthy, neurosonological categorization according to the STOP protocol did not show relevant differences between these two groups. Conversely, higher TAMMVs in the posterior circulation vessels were documented in patients with ischemic lesions, namely in the left PCA and in the Top of BA (Supplementary Table 1).

This cross-sectional study has shown that the posterior border-zone of SCA patients is often affected by SCIs, with frequent bilateral involvement. In these patients, cerebral hemodynamics appear altered with an increased rate of PCA stenosis and increased blood flow velocities.

One interesting finding of our study is the significant rate of posterior circulation involvement, with 19.6% of patients showing SCIs in the posterior border-zone, bilaterally in 47% of them. Surprisingly, a larger lesion burden - albeit not statistically significant - was observed in these regions compared with anterior border-zone lesion burden. There is a lack of data on this topic. In the SIT Trial, only 15/164 (9.1%) SCIs were located in the posterior border-zone, which differs from the data presented here.[18] However, our results are similar to those obtained by Kwiatkowski et al. who found a 27.7% prevalence of SCIs, with 31.2% lesions located in posterior circulation areas.[10] These controversial observations indicate that we need to gain more knowledge on this topic, as the majority of studies have focused on anterior circulation infarcts and vasculopathy.

Regarding the MRA findings, 9.2% of our cohort exhibited at least one stenosis in the posterior cerebral circulation, exclusively involving the PCAs. Bilateral stenoses were present in 62.5% of these cases. In contrast, previous studies that also examined the posterior circulation reported either a few cases of stenosis, even when strokes occurred in that region, or no vasculopathy at all. [11-13]

Interestingly, we found a significant association between the detection of PCA stenosis and ipsilateral SCIs in the posterior border-zone. While anterior intracranial vasculopathy is a known predictor of stroke and silent infarcts in SCD, most studies have not examined the consistency between MRA stenoses and MRI ischemic lesions[10]. Similarly, the SIT Trial linked MRA-defined vasculopathy with SCIs, but found no relationship between the stenosis and infarct sides. Our study is the first to explore vascular lesions in the posterior border-zone alongside ipsilateral middle or posterior cerebral artery stenosis. Notably, nearly two-thirds of posterior circulation lesions lacked consistent vascular stenosis, suggesting other mechanisms may contribute to SCIs.[13]

In our cohort, we did not find an association between the STOP categories and cerebral ischemic burden in the posterior cerebral circulation. These results suggest that the currently adopted neurosonological classification of SCA patients is not an efficient tool to identify those with silent ischemic lesions in the cerebral posterior circulation. Interestingly, we found a significant increase in blood flow velocities in the left PCA and Top of BA. Available data regarding posterior circulation velocities are scant; however, the majority of studies on the anterior circulation did not find a relationship between increased blood flow velocities and the presence of silent ischemic infarcts.[10]

Despite prospectively collected data, our study has limitations. First, TCD was performed by different operators over an extended period, potentially affecting reproducibility. However, all operators were fully certified, and this limitation is common in real-world studies. Second, around 21% of ultrasound exams were incomplete, which could impact the final analysis; however, incomplete results are not linked per se to an increased risk of cerebrovascular disease.[14-15]

In conclusion, analysis of data from this long-term longitudinal pediatric cohort of SCA patients has shown a significant cerebral ischemic burden involving the posterior border-zones, with an increased rate of PCA stenosis and elevated blood flow velocities. Current STOP criteria do not seem to be an effective tool when applied to posterior circulation.

REFERENCES

1. Piel FB, Rees DC, DeBaun MR, et al. Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission. Lancet Haematol. 2023;10(8):e633-e686.
2. Stotesbury H, Kawadler JM, Hales PW, Saunders DE, Clark CA, Kirkham FJ. Vascular Instability and Neurological Morbidity in Sickle Cell Disease: An Integrative Framework. Front Neurol. 2019;10:871.
3. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339(1):5-11.
4. Kwiatkowski JL, Voeks JH, Kanter J, et al; Post-STOP Study Group. Ischemic stroke in children and young adults with sickle cell disease in the post-STOP era. Am J Hematol. 2019;94(12):1335-1343.
5. Reggiani G, Coppadoro B, Munaretto V, et al. Relationship between hemoglobin, hemolysis, and transcranial Doppler velocities in children with sickle cell disease: Results from a long-term natural history study in Italy in the era of multimodal therapy. Eur J Haematol. 2023;111(3):414-422.
6. Bernaudin F, Verlhac S, Arnaud C, et al. Chronic and acute anemia and extracranial internal carotid stenosis are risk factors for silent cerebral infarcts in sickle cell anemia. Blood. 2015;125(10):1653-1661.
7. Montanaro M, Colombatti R, Pugliese M, et al. Intellectual function evaluation of first generation immigrant children with sickle cell disease: the role of language and sociodemographic factors. Ital J Pediatr. 2013;39:36.
8. Marcon V, Meneghetti G, Rampazzo P, Ermani M. 107. Ultrasound investigations in sickle cell anemia. Initial assessment and follow up. Clinical Neurophysiology. 2013;124(11):e213.
9. Houkin K, Nakayama N, Kuroda S, Nonaka T, Shonai T, Yoshimoto T. Novel magnetic resonance angiography stage grading for moyamoya disease. Cerebrovasc Dis. 2005;20(5):347-354.
10. Kwiatkowski JL, Zimmerman RA, Pollock AN, et al. Silent infarcts in young children with sickle cell disease. Br J Haematol. 2009;146(3):300-305.
11. Adegoke SA, Figueiredo MS, Vicari P, et al. Posterior Circulation Evaluation in Patients with Sickle Cell Anemia. J Stroke Cerebrovasc Dis. 2016;25(3):717-721.
12. de Blank PMK, Hayward DM, Zimmerman R, Pollock A, Kwiatkowski JL. Transcranial Doppler Ultrasound Velocity, Cerebral Vasculopathy, and Silent Infarcts In Sickle Cell Disease. Blood. 2010;116(21):269.

13.Linguet SL, Verlhac S, Missud F, et al. Stroke without cerebral arteriopathy in sickle cell disease children: causes and treatment. Haematologica. 2024;109(10):3346-3356.
14. Voi V, Gutierrez-Valle V, Cuzzubbo D, et al. Limited access to transcranial Doppler screening and stroke prevention for children with sickle cell disease in Europe: Results of a multinational EuroBloodNet survey. Pediatr Blood Cancer. 2024:e31190.
15. Kanter J, Phillips S, Schlenz AM, et al. Transcranial Doppler Screening in a Current Cohort of Children With Sickle Cell Anemia: Results From the DISPLACE Study. J Pediatr Hematol Oncol. 2021;43(8):e1062-e1068.

TABLES

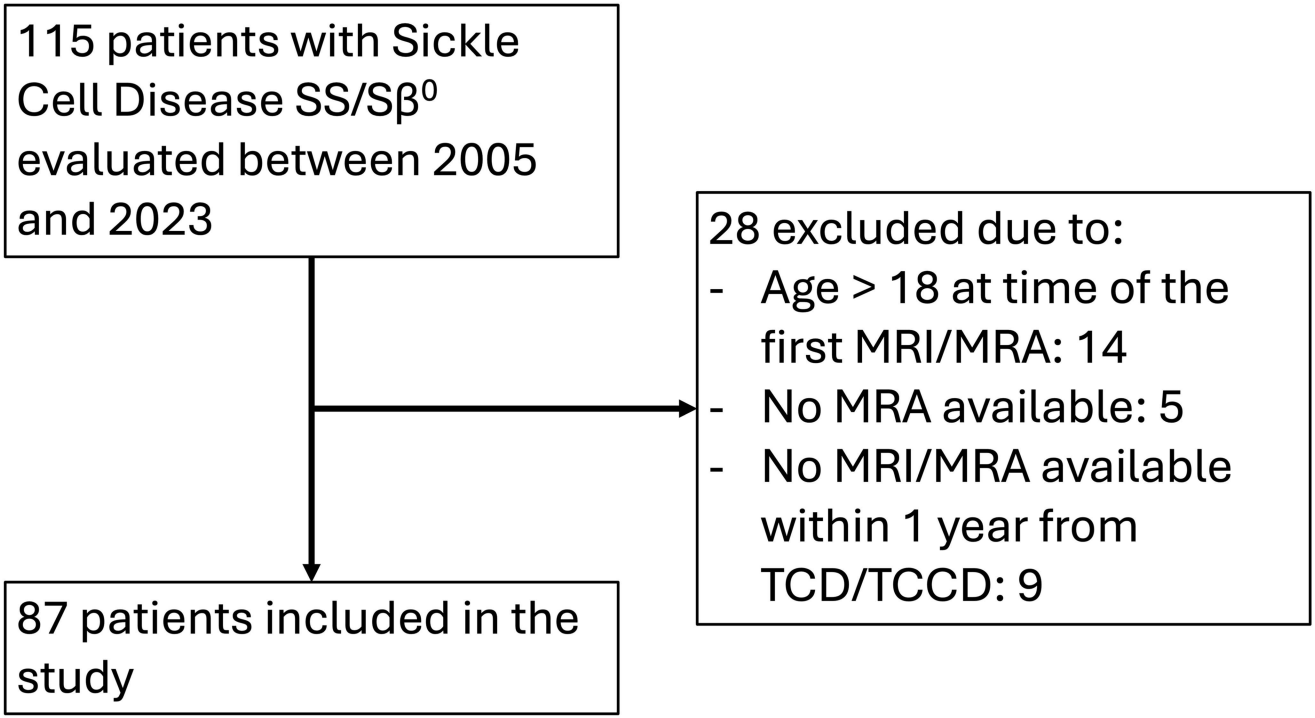
Table 1 - Baseline characteristics of the children with Sickle Cell Anemia included in the study. Hb, hemoglobin; STOP, Stroke Prevention Trial; PCA, posterior cerebral artery; BA, basilar artery

	Study Population n = 87
Demographic and clinical data	
Age (years), *median (IQR)*	10 (6.7-13.4)
Female, *n (%)*	43 (49.4)
Hb Genotype, *n (%)*	
Hb SS	83 (94.3)
Hb Sβ°	5 (5.7)
Hemoglobin (g/dL), *median (IQR)*	8.7 (8.1-9.8)
Ongoing Therapy, *n (%)*	
None	22 (25.2)
Hydroxyurea	55 (63.2)
Chronic blood transfusion	5 (5.7)
Cerebrovascular events, *n (%)*	0
History of Acute Chest Syndrome, *n* (%)	43 (49.4)
History of Splenic sequestration, *n (%)*	11 (12.6)
Neurosonological data	
STOP Trial Categories, *n (%)*	
Normal	46 (52.9)
Low Flow	16 (18.4)
Conditional	5 (5.7)
Abnormal	1 (1.1)
Incomplete Examination	19 (21.8)
Posterior circulation vessels adequately insonated, *n (%)*	
Right PCA	76 (87.4)
Left PCA	75 (86.2)
BA	73 (83.9)
Top of BA	68 (78.2)

Table 2 - Neuroradiological characteristics of patients and vascular territories. MCA: middle cerebral artery; PCA: posterior cerebral artery

		Study Population n = 87	
Patients with Cerebral ischemic lesions	*n (%)*	25 (28.7)	
Anterior border zone only	*n (%)*	8 (9.2)	
Posterior border zone only	*n (%)*	3 (3.4)	
Anterior and posterior border zones	*n (%)*	14 (16.1)	
Lesions in other sites	*n (%)*	1 (1.1)	
Patients with Intracranial stenosis	*n (%)*	42 (48.3)	
Anterior circulation only	*n (%)*	34 (39.1)	
Posterior circulation only	*n (%)*	2 (2.3)	
Anterior and posterior circulation	*n (%)*	6 (6.9)	
Ischemic burden, volume (cc), *median (IQR)*		**p value**	
Anterior circulation (34 territories)	60.5 (34.4-736)	0.244	
Posterior circulation (25 territories)	264 (66.0-754)		
Posterior border-zone regions		**n = 176**	**p value**
- Territories with Ischemic lesions, *n (%)*		25 (14.2)	
- MCA stenosis with ipsilateral lesion, *n (%)*		5/29 (17.2)	0.62
- PCA stenosis with ipsilateral lesion, *n (%)*		7/13 (53.8)	<0.0001

Figure 1. Study Design with Inclusion and Exclusion Flow Chart. MRI: Magnetic Resonance Imaging; MRA: Magnetic Resonance Angiography; TCD: Transcranial Doppler; TCCD: Transcranial Color Coded Doppler

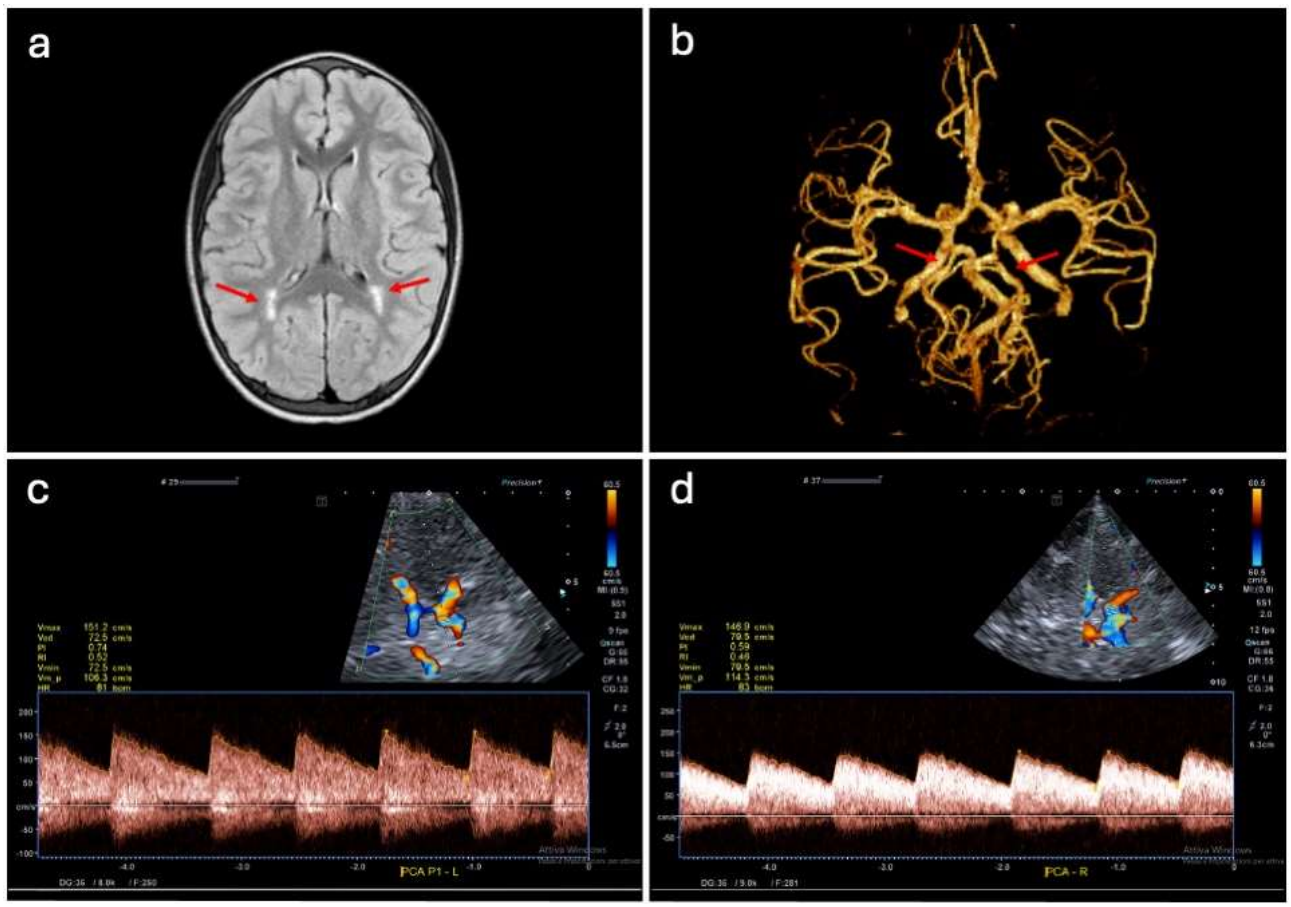

115 patients with Sickle Cell Disease SS/Sβ0 evaluated between 2005 and 2023
28 excluded due to:
- Age > 18 at time of the first MRI/MRA: 14
- No MRA available: 5
- No MRI/MRA available within 1 year from TCD/TCCD: 9
87 patients included in the study

Supplementary Table 1. Comparison of hematological, neuroradiological and neurosonological data. ACS: Acute Chest Syndrome.

	Patients with posterior ischemic lesions	**Patients without posterior ischemic lesions**	**p value**
	n = 17 (19.6%)	**n = 70 (80.4%)**	
Age (years), *median (IQR)*	10.8 (7.95-13.2)	10 (6.6-13.4)	0.895
Hemoglobin at TCCD *(g/dL), median (IQR)*	8.6 (8.1-9.5)	8.7 (8.2-9.9)	0.387
History of ACS and/or spleen sequestration crisis, *n (%)*	10 (58.8)	39 (55.7)	0.668
History of ACS and/or spleen sequestration crisis, episodes per patient, *median (IQR)*	1 (0-3)	1 (0-2)	0.352
Therapy, *n (%)*			
Hydroxyurea	7 (41.2)	48 (68.6)	0.05
Chronic blood transfusions	2 (11.8)	3 (4.3)	0.251
Intracranial stenosis, *n (%)*	9 (52.9)	33 (47.1)	0.788
PCA stenosis, *n (%)* PCA stenosis, *n of arteries (%)**	4 (23.5) 8 (23.5)	4 (5.7) 5 (3.6)	0.042 0.002
STOP Trial Categories, *n (%)*			0.206
Normal	10 (58.8)	36 (51.4)	
Conditional	1 (5.9)	4 (5.7)	
Abnormal	1 (5.9)	0	
Low Flow	1 (5.9)	15 (21.4)	
Incomplete Examination	4 (23.5)	15 (21.4)	
TAMMV at TCCD *(cm/s), median (IQR)*			
Right PCA	76.0 (67.0-84.8)	69.5 (57.0-84.4)	0.481
Left PCA	81.0 (72.0-95.0)	68.2 (53.5-88.0)	0.048
BA	74.0 (66.0-80.0)	67.0 (54.0-78.0)	0.078
Top of BA	81.0 (42.0-89.0)	52.0 (38.5-70.0)	0.040

*Total PCAs: 34 in 17 patients with posterior ischemic lesions vs 140 in 70 patients without posterior ischemic lesions

Supplementary Figure 1. Neuroimaging in a child with Sickle Cell Anemia and posterior circulation involvement. a) MRI, arrows indicate posterior ischemic lesions; b) MRA, arrows indicate bilateral Posterior Cerebral Artery (PCA) stenosis; TCCD (c-d), increased blood flow velocities in the PCAs bilaterally



Supplementary Figure 2. Neuroimaging in a child with Sickle Cell Anemia without posterior circulation involvement. a) MRI; b) MRA; c-d) TCCD.