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

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) has significantly improved long-term survival and disability.[3-5] However, silent cerebral infarcts (SCI) with a prevalence of 39% by the age of 18 years 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 1, 2005 to May 6, 2023. A clinical and hematological assessment was completed every 3 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] Brain magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) was performed every 2 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 1 vessel), abnormal (TAMMV >200 cm/s in at least 1 vessel), low flow (TAMMV <70 cm/s in at least 1 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 (IQR), while categorical data as number and percentage. Mann-Whitney U test, Pearson χ^2 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 and 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 or 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 eight (9.2%) (*Online Supplementary Figures S1, S2*). Selective posterior border-zone involvement was observed in three (3.4%) children. Surprisingly, the posterior border-zone lesion burden was not inferior to the anterior one (median volume 264 cc [IQR, 66-754] *vs*. 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 eight children (9.2%): all of them involved the PCA, bilaterally in five (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 seven of 25 (28%). Interestingly, the presence of a PCA

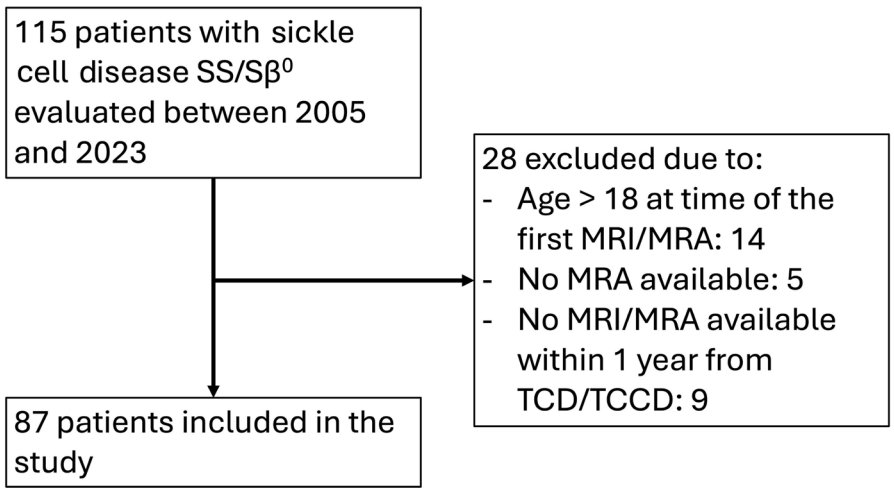

Figure 1. Study design with inclusion and exclusion flow chart. MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; TCD: transcranial Doppler; TCCD: transcranial color-coded Doppler.

stenosis was associated with an ipsilateral ischemic lesion in the posterior border zones in seven of 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 *Online Supplementary Table S1*, 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 PCA in 17 patients with posterior lesions, 23.5% *vs*. 6/140 PCA 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 TAMMV in the posterior circulation vessels were documented in patients with ischemic lesions, namely in the left PCA and in the top of BA (*Online Supplementary Table S1*).

This cross-sectional study has shown that the posterior border zone of SCA patients is often affected by SCI, with frequent bilateral involvement. In these patients, cerebral hemodynamics appears 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 SCI 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 of 164 (9.1%) SCI 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 SCI, 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 PCA. 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

Table 1. Baseline characteristics of the children with sickle cell anemia included in the study.

	Study population N=87
Demographic and clinical data	
Age in 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)
Hb 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)

Hb: hemoglobin; STOP: Stroke Prevention Trial; PCA: posterior cerebral artery; BA: basilar artery; IQR: interquartile range.

Table 2. Neuroradiological characteristics of patients and vascular territories.

	Study population N=87	*P*
Patients with cerebral ischemic lesions, N (%)	25 (28.7)	-
Anterior border zone only	8 (9.2)	-
Posterior border zone only	3 (3.4)	-
Anterior and posterior border zones	14 (16.1)	-
Lesions in other sites	1 (1.1)	-
Patients with Intracranial stenosis, N (%)	42 (48.3)	-
Anterior circulation only	34 (39.1)	-
Posterior circulation only	2 (2.3)	-
Anterior and posterior circulation	6 (6.9)	-
Ischemic burden volume in cc, median (IQR)		
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	-
Territories with Ischemic lesions	25/176 (14.2)	-
MCA stenosis with ipsilateral lesion	5/29 (17.2)	0.62
PCA stenosis with ipsilateral lesion	7/13 (53.8)	<0.0001

MCA: middle cerebral artery; PCA: posterior cerebral artery; IQR: interquartile range.

region, or no vasculopathy at all.[11-13]

Interestingly, we found a significant association between the detection of PCA stenosis and ipsilateral SCI 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 SCI, 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 SCI.[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.

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Contributions

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

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Data-sharing statement

Data are available on request addressed to the corresponding author.

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