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Hemodynamic profile of cerebral arteries using transcranial Doppler in children with sickle cell disease compared to children without sickle cell disease: *Prospective analytical study*

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Abstract

Background Cerebral vasculopathy is a frequent and serious complication of major sickle cell disease syndromes. Transcerebral Doppler (TCD) can detect stenosis of the main arteries at the base of the skull before stroke occurs, and initiate therapy to avoid complications. The objective of the study is to evaluate and compare the hemodynamic profile of the middle cerebral artery using TCD in children with sickle cell disease compared to children without sickle cell disease.

Method Prospective analytical study extended over a 6-month period from July 04, 2023 to December 28, 2023. The study population consisted of subjects followed for homozygous sickle cell disease SS and non-sickle cell subjects received at the above-mentioned centers, of all sexes, aged 2 to 16 years at most.

Results We recruited 182 children (52.2% male and 47.8% female) divided into 70 children with sickle cell disease and 112 children without sickle cell disease. The mean of Maximum systolic velocity (MSV) on the left was 85.0 ± 49.5 cm/s in sickle cell patients and 84.5 ± 17.8 cm/s in non-sickle cell patients. The mean of telediastolic velocity (TDV) was 40.9 ± 31.2 cm/s in sickle cell patients and 44.0 ± 15.8 cm/s in non-sickle cell patients. The mean maximum velocity (MMV) was 53.22 ± 39.0 cm/s in sickle cell patients and 57.5 ± 16.3 cm/s in non-sickle cell patients.

Conclusion The mean velocity of children with sickle cell disease was lower than that of non-sickle cell patients, and the peak systolic velocity of children with sickle cell disease was slightly higher than those of children without sickle cell disease.

Keywords Cerebral vasculopathy, Sickle cell disease, Stroke, Transcranial Doppler, Child

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Introduction

Cerebral vasculopathy is a frequent and serious complication of major sickle cell syndromes (SS and Sβ° thal homozygous sickle cell disease) [1–4]. It has therefore been extensively studied, particularly in children. Indeed, it is in the pediatric age that stenosing cerebral vasculopathy develops in sickle cell children, and particularly before the age of 10. The risk of cerebral infarction in these patients is particularly high, more than 300 times that of the general pediatric population [5–7]. These cerebral arterial infarcts may be clinically symptomatic, with predominantly motor or cognitive signs [8, 9]. They can also be so-called silent infarcts, but statistically associated with cognitive impairment. The risk of disability is therefore high in these patients, as is the risk of stroke recurrence [10, 11]. Cerebral vasculopathy is detected by transcranial Doppler (TCD), the gold standard. Several studies have shown that transcranial doppler ultrasonography (EDTC) is an effective tool for predicting the risk of stroke in children with sickle cell disease. Depending on the results of the examination, treatment can be adapted to reduce this risk, for example by prescribing regular blood transfusions or administering anticoagulant therapy [12–16]. In the Democratic Republic of Congo, transcranial doppler ultrasonography (EDTC) is not widely used, despite the increasing prevalence of sickle cell disease, which has risen from 1.4% in 2011 to at least 2% in 2020, with high cardiovascular and renal mortality [17]. In this respect, early detection and management of sickle cell disease may contribute to reducing sickle cell-related mortality. The overall aim of this study is to evaluate and compare the hemodynamic profile of the middle cerebral artery on transcranial Doppler in children with sickle cell disease compared with children without sickle cell disease.

Methods

This was a prospective analytical study conducted over a 6-month period, from July 4, 2023 to December 28, 2023, at the Saint Crispin "Anémique SS" Hospital (C.H.C) and at the "Cliniques Du Coeur ONGD" (LCC) imaging and diagnostic center.

The study population consisted of subjects with homozygous SS sickle cell disease and non-sickle cell subjects seen at the above-mentioned centers, of all sexes, aged 2 to 16 years maximum. Sampling was non-probabilistic, based on consecutive recruitment of patients and non-patients. The sample size was 70 homozygous SS sickle cell cases. We added a control group of 112 non-sickle-cell AA cases. The matching criteria were age and sex. We included in group 1, children aged up to 16 years, identified and biologically confirmed sickle cell disease of the SS homozygous phenotype, not receiving blood transfusion treatment during the study period, using stratified random sampling (boys and girls); in group 2, children aged up to 16 years, non-sickle cell disease, not suffering from any acute or chronic condition, including boys and girls were recruited using stratified random sampling with informed parental consent. To carry out the survey, we used a data collection form adapted from standard literature forms, to which additional questions were added. The form is divided into 2 parts, the first for socio-demographic information and the laboratory analysis report, and the second for the TCD report.

The sociodemographic section includes the following information: age (date of birth), sex, transfusion history, date of last transfusion. The para-clinical section includes the following information biology: blood group, electrophoresis, hemoglobin level (g/dl), hematocrit level (%) and mean corpuscular volume (MCV) in fl.

Ultrasound and Doppler parameters including arteries: left middle cerebral artery, right middle cerebral artery and recorded and observed parameters: presence of temporal window and arterial flow, maximum systolic velocity (MSV), telediastolic velocity (TDV), mean maximum velocity (MMV), pulsatility index and resistance index. We used a PHILIPS ClearVue 850 multi-frequency ultrasound scanner, manufactured in 2015 and commissioned in September 2021, for our DTC examinations. We used a 2 MHz sectorial (cardiac) probe. The TCD was performed and interpreted by a single radiologist for better and more uniform results.

Operational defintions

The temporal path was used to record the spectra of the cerebral arteries. The examination began in B mode, with the identification of certain anatomical echo landmarks, notably the cerebral peduncles, the large wing of the sphenoid and the Sylvian valley.

The filters were set appropriately (from 10 to 100 MHz) so as not to miss slow flows. The PRF was adjusted manually according to the quality of the trace obtained and the speeds observed (up to 20 kHz). The incidence of the ultrasound beam in relation to the vessel studied was less than 30. The Doppler gate was positioned as far as possible in the center of the vessel to be studied, with an opening of 3.5 mm. Each intra-cerebral vessel was explored.

After manual tracing, we recorded the values obtained for each MCA (left and right): maximum systolic velocity (MSV), telediastolic velocity (TDV) and mean maximum velocity (MMV).

The mean systolic velocity of the middle cerebral arteries was considered normal if it was less than 170 cm/s in children with sickle cell disease and 65 cm/s in children without sickle cell disease, and the pulsatility index (PI) was considered normal for values between 1.16 and 1.24.

Statistics analysis

Data entry was carried out using Microsoft Excel 2010 for Windows; data were then stored on the Kobocollect application, followed by statistical analysis of the data using STATA 15 software. Descriptive statistics were presented as mean (plus or minus standard deviation) for continuous variables with a normal distribution. The normality test (Kolmogorov–Smirnov or Shapiro–Wilk) was used to differentiate between normally and non-normally distributed quantitative variables. Absolute (n) and relative (%) frequencies were expressed for categorical variables. Student's t-test and Pearson's Chi-square or Fischer's exact test were performed, respectively, to compare means and proportions in the two groups. The simple linear correlation test was used to analyze and compare the two groups. The significance level used to determine a statistically significant difference was $p < 0.05$.

Results

Distribution of children by sex in the two groups

We have 70 sickle cell patients, 54.3% male and 45.7% female, as well as 112 non-sickle cell patients, 50.9% male and 49.1% female (Fig. 1).

The distribution is not homogeneous for the two population groups ($p = 0.125$) with an average age of 10.0 ± 4.3 years for children with sickle cell patients and 10.7 ± 4.3 years for children without sickle cell patients no difference in average age (Table 1).

The majority of children with sickle cell disease had a hemoglobin level below 11 g/dl with extremes of 5 and 9.6 g/dl. All children with sickle cell disease had a hematocrit level below 30% with extremes of 15.1 and 28.1% (Fig. 2).

This figure shows that 67.1% of children with sickle cell disease had all vessels insonated, compared with 75.9% of children without sickle cell disease (Fig. 3).

We note that on the permeability of the vessels of the polygon of Willis and the basilar trunk in general. MCA is visible in all children examined, i.e. 100% of cases (sickle cell and non-sickle cell patients). In children with sickle cell disease, we also note more visibility of the posterior cerebral artery in 92.1% of cases, followed by the basilar trunk and the internal carotid artery (Table 2).

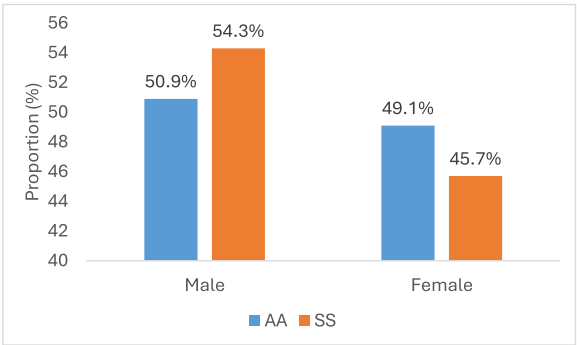

Fig. 1 Gender distribution diagram

Table 1 Distribution according to age group

Age	All n(%)	No Sickle cell patients n(%)	Sickle cell patients n(%)
Mean age ± SD	10.3 ± 4.3	**10.7 ± 4.3 ans**	**10.0 ± 4.3 ans**
< 5 years	22(12.1)	11(9.8)	11(15.7)
5–7 years	25(13.7)	19(17.0)	6(8.57)
8–10 years	41(22.5)	21(54.5)	20(28.6)
> 10 years	94(51.7)	61(54.6)	33(47.1)

In this series, mean left MSS was 85.0 ± 49.5 cm/s in sickle-cell patients and 84.5 ± 17.8 cm/s in non-sickle-cell patients. Mean EDS was 40.9 ± 31.2 cm/s in sickle cell patients and 44.0 ± 15.8 cm/s in non-sickle cell patients. Mean AMS was 53.22 ± 39.0 cm/s in sickle cell patients and 57.5 ± 16.3 cm/s in non-sickle cell patients. Mean right MSS was 81.3 ± 49.5 in sickle cell patients and 80.9 ± 17.4 in non-sickle cell patients. Mean EDS was 38.6 ± 27.3 in sickle cell patients and 41.5 ± 14.8 in non-sickle cell patients. The mean AMS was 51.1 ± 35.5 in sickle cell patients and 54.3 ± 16.0 in non-sickle cell patients. Resistance index values in sickle cell patients were discretely higher than in non-sickle cell patients. Even if the difference is minimal, this is observed on both sides of the temporal window. The same remarks on resistance indices also apply to pulsatility indices. Children with sickle cell disease have a higher pulsatility index overall (Table 3).

The correlation coefficient between mean speed and the variables Hb and Hct is negative, which means that in our series, if these two variables decrease, speed also decreases. As for MCV, the correlation coefficient is positive. When MCV increases, speed increases (Table 4).

Discussion

The aim of the present study was to evaluate and compare the hemodynamic profile of the middle cerebral artery on transcranial Doppler in children with sickle cell disease versus children without sickle cell disease. In our study, the middle and posterior cerebral arteries are the easiest to visualize via the temporal route. The middle cerebral artery was visualized in 100% of cases in both sickle cell and non-sickle cell patients. The posterior cerebral artery is seen in more than 92% of cases in children with sickle cell disease, and in more than 81% of cases in children without sickle cell disease. In contrast to these

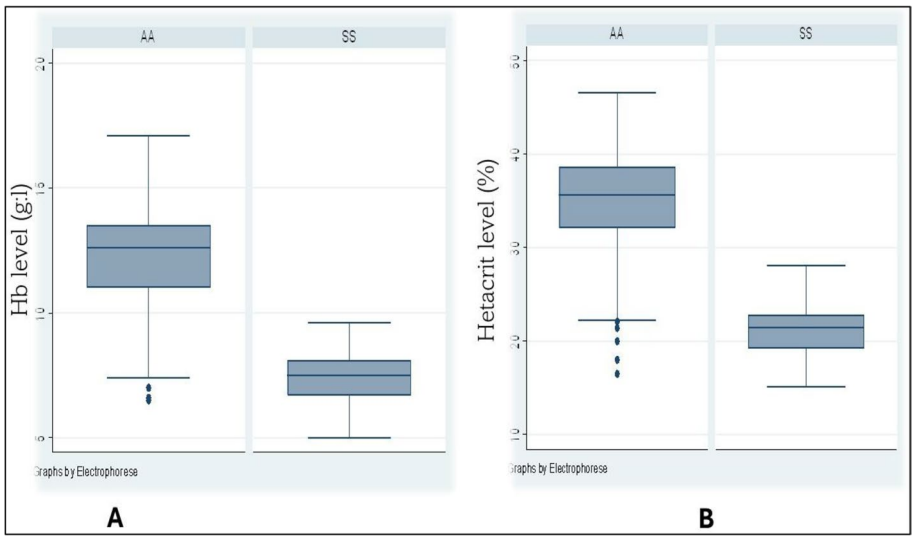

Fig. 2 Graph of the distribution of children according to Hb level (**A**) and to the hematocrit level (**B**)

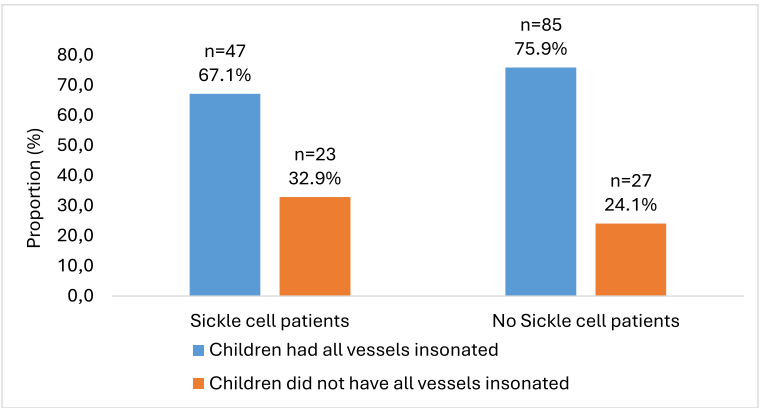

Fig. 3 Proportion of children with all vessels insonated

two arteries, the anterior cerebral artery is the most difficult to study.

These results concur with those of Herijoelison Andry Roussel in Madagascar in 2012, who during a six-month study on transcranial doppler during sickle cell disease in Malagasy children, with a sample of 100 children divided into 57 sickle cell children and 43 non-sickle cell children, found that the posterior cerebral artery was seen in over 91% of cases in sickle cell children and in 79% of cases in non-sickle cell children [18]. Visualization of middle cerebral artery flow is of paramount importance in assessing the risk of cerebral ischemia. Indeed, in the presence of a satisfactory temporal window with good visualization of ultrasound landmarks, the impossibility of recording middle cerebral artery flow when the other arteries are recordable is an additional marker of stroke risk [19].

Mean and maximum systolic velocity

The mean velocity of children with sickle cell disease was lower than that of children without sickle cell disease, and the maximum systolic velocity of children with sickle cell disease was slightly higher than that of children without sickle cell disease. This can be explained by the brain vascular response to compensate the chronic hypoxia resulting from the chronic anemia status [20]. A study done on 145 Nigerian children with sickle cell anemia has found that the mean velocities in children with HbSS was 152 ± 27 cm/s, [21] which is much higher than our patients (103 ± 30.6 and 106 ± 27.4 cm/s). There is no clear explanation for this difference, but one probability is that the Nigerian study was done on patients carrying HbSS hemoglobin type; while the phenotype of hemoglobin was not one of the inclusion criteria of our study,

Table 2 Proportion of the presence of temporal window and flow of each artery on the left side in the two population groups

Variables	No Sickle cell patients n(%)	Sickle cell patients n(%)
Left window		
MCA	112(100.0)	70(100.0)
ACA	43(38.4)	47(67.2)
LCA	85(75.6)	53(75.4)
PCA	89(79.4)	64(92.1)
BT	65(58.0)	62(88.0)
Right window		
MCA	112(100.0)	70(100.0)
ACA	43(38.4)	38(54.2)
LCA	85(75.6)	50(72.1)
PCA	91(81.4)	64(92.1)
BT	65(58.0)	62(88.0)

MCA Middle cerebral artery, *ACA* Anterior cerebral artery, *LCA* Lower cerebral artery, *PCA* Posterior cerebral artery, *BT* branchial trunk

patients with HbSC hemoglobin who can represent a part of our sample usually have milder disease than patients with HbSS.

According to the literature, the mean and maximum systolic velocities of children with sickle cell disease are significantly higher than those of children without sickle cell disease [22, 23]. Mean velocities in excess of 140 cm/s were only found in 2 children with sickle cell disease. In the study carried out by Hokazono in 2011 in the Sao Paulo region of Brazil, the average speed was 1.6% [24]. A study of 358 SS homozygous children in 2014 in Bamako, Mali by A Dorie et al., found 17.3% borderline DTC and 8.1% pathological TCD [25]. According to Verlhac et al., the frequency of pathological TCD examinations among SS children is around 10% and that of borderline examinations 9% [16]. The risk of occurrence of a velocity greater than 2 m per second is very significantly related to SS and Sbeta0 phenotype, to the degree of anemia assessed by basal hemoglobin level at a distance from a vaso-occlusive crisis and a transfusion, to high MCV (no risk in case of GMV less than 75 in the absence of iron or folate deficiency), and to the absence of alpha-deletion. A study carried out by Inoussa BD et al. in 2022 on the velocimetric profile of sickle-cell patients at three different sites in the city of Niamey, Niger, reported that the risk of vasculopathy was high in 68.15% of cases, intermediate in 9.63% and low in 14.81% [26]. These abnormal and conditional results are only recorded at the level of the middle cerebral artery, according to the data in the publication. In a BABY HUG study of 192 sickle cell children with an average age of 12.6 months, the average velocity encountered was 115 cm/s, which is considerably lower than the average velocities of older sickle cell children, which is approximately 140 cm/s. And no child in this BABY HUG study had an abnormal result as defined in older children (≥200 cm/s) [27]. This suggests that the screening program should start at an earlier age, and that a cut-off point for stroke risk should be established for this age group. The resistance and pulsatility indices are discreetly higher in our sickle cell patients. Although the difference is minimal, this finding can be observed on both sides of the temporal window. Sonhaye L et al. have reported that recorded pulsatility indices show a discrete decrease in values in sickle cell children, with a statistically significant difference (p-value = 0.02) [28, 29]. Our results are consistent with previous studies, in that

Table 4 Correlation between hemodynamic parameters and the Mean Velocity of the MCA

Variable	No Sickle cell		Sickle cell	
	r	*p*-value	r	*p*-value
Age	0,1181	0,215	0,1902	0.1148
Hb level	0,1683	0,0762	−0,4865	**< 0.001**
Hematocrit level	0,1658	0,0807	−0,4292	**0.002**
MCV	−0,1497	0,1151	0,4469	**0 .001**

Hb Hemoglobin, *MCV* Mean corpuscular volume

Table 3 Assessment of MCA blood flow velocity

Variable	Right			Left		
	No Sickle cell	Sickle cell	p	No Sickle cell	Sickle cell	p
MSS	84.5 ± 17.8	85.0 ± 49.5	0.900	80.9 ± 17.4	81.3 ± 49.5	**0.932**
EDS	44.0 ± 15.8	40.9 ± 31.2	0.342	41.5 ± 14.8	38.6 ± 27.3	**0.385**
AMS	57.5 ± 16.3	53.22 ± 39.0	0.341	54.3 ± 16.0	51.1 ± 35.5	**0.453**
Resistance index	0,49 ± 0,23	0,55 ± 0,22	0.015	0,49 ± 0,15	0,55 ± 0,24	0.002
Pulsatility index	0,81 ± 0,15	1,18 ± 0,15	0.007	0,79 ± 0,19	0,98 ± 0,19	< 0.001

MSS maximum systolic speed, *EDS* end-diastolic speed, *AMS* average of the maximum speeds

Correlation between hemodynamic parameters and the Mean Velocity of the ACM in the two groups (correlation coefficient and *p*-value)

mean velocity values do not vary with mean corpuscular volume at the level of the middle cerebral artery. In our study, the coefficient of relationship between GMV and VMT is positive. In other words, as GMV increases, so does velocity. Nevertheless, among the risk factors for velocity above 200 cm/s, Verlhac suggests that a high blood volume is one of them, and consequently, a blood volume below 75 fl confirms the absence of this risk.

One limitation of this study is that only one transcranial Doppler study was referenced without any description of a previous transcranial Doppler. There can be natural variations in transcranial Doppler measurements.

Conclusion

This study showed that the hemodynamic profile of the middle cerebral artery on transcranial Doppler in children with sickle cell disease compared with children without sickle cell disease did not differ significantly. However, this study showed that among vessels insonated, mean maximum velocity varied as a function of hemoglobin level, hematocrit and mean corpuscular volume.

Abbreviations

MCA	Middle cerebral artery
ACA	Anterior cerebral artery
LCA	Lower cerebral artery
PCA	Posterior cerebral artery
BT	Branchial trunk
TCD	Transcranial Doppler
MSS	Maximum systolic speed
EDS	End-diastolic speed
AMS	Average of the maximum speeds
Hb	Hemoglobin
MCV	Mean corpuscular volume

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Authors' contributions

PLA conceptualized the research topic, ANN drafted the protocol, JTM enhanced and validated the protocol, AAN prepared the submission for institutional review board approval, JKM, OMY, RIG, LM, EM, DMI and LM supervised the data collection and drafted the manuscript. ANN carried out the statistical analysis with guidance from PLA. CBM, STY, AAM and JTM reviewed the first draft of the manuscript. All authors provided conceptual input, revised, and approved the final version of the manuscript.

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Data availability

The datasets analyzed during this study are available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the National Health Ethics Committee at No 468/CNES/PN/PMMF/2023. The procedures were conducted in accordance with the ethical standards set forth by the Committee on Human Experimentation and the Helsinki Declaration of 1964, as revised in 2013. Given that this retrospective study utilized de-identified patient data, there was no potential for harm or impact on patient care. Therefore, informed consent was waived. This waiver was approved by the institutional review board and ethics committee of our institution in accordance with regulatory and ethical guidelines pertaining to retrospective studies.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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