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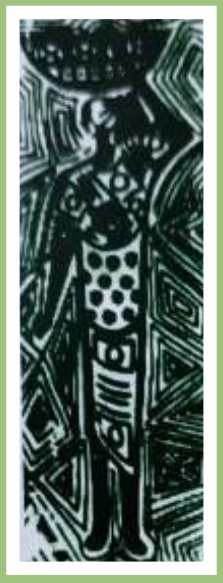

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Cerebral Artery Blood Flow Velocities in Children with Sickle Cell Anaemia at the Federal Teaching Hospital, Owerri

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Abstract

Introduction: Vaso-occlusion in Sickle Cell Anaemia (SCA) results in the narrowing of the major cerebral blood vessel, predisposing affected children to cerebrovascular accidents (CVA). The risk of CVA can be assessed with cerebral blood flow velocities measurement using a transcranial Doppler ultrasound.

Objective: To determine the cerebral blood flow velocities in children with SCA aged 2-16 years.

Methods: This was a hospital-based, cross-sectional study of children with SCA conducted between April and September 2023. Transcranial Doppler ultrasound was used to assess the anterior and middle cerebral arteries.

Results: A total of 102 children out of the 150 enrolled were screened within the study period. The values obtained from this procedure were categorised as abnormal (≥200cm/s), conditional (170 – 199cm/s) and normal or standard risk (< 170cm/s). Children with abnormal blood velocities are at high risk of CVA, while children whose velocities fall within the conditional range are at moderate risk for CVAs. The prevalence of abnormal cerebral blood flow velocity above 170cm/second was 17.6% (13.7% was in the conditional risk zone and 3.9% in the high-risk zone). All the subjects in the high-risk zone were aged 2-6 years, and 75% were females.

Conclusion: The prevalence of abnormal cerebral blood flow velocity in the cohort of SCA children is 17.6%, with 10-40% annual risk for stroke. Identification of children at risk for a CVA helps in the primary prevention of CVA by prompt therapy institutions.

Keywords: Cerebral Blood Flow Velocity, Cerebrovascular Accident, Sickle Cell Anaemia, Stroke, Transcranial Doppler Ultrasound.

Introduction

Sickle Cell Disease (SCD) is a genetic disorder resulting from a point mutation in the beta chain of haemoglobin where hydrophilic glutamic acid is replaced by hydrophobic valine.[1] With almost 305,000 live births annually, SCD is the most common genetic haematological disorder worldwide.[2] Sickle cell disease affects 20-25 million people globally, with 75% of these residing in Africa, especially in malaria-endemic areas like Nigeria, Senegal, and Madagascar.[3] Sickle cell anaemia (SCA) affects up to 2% of the global population; 90% of this global population resides in Nigeria, India and the Democratic Republic of Congo.[4]

Complications of SCA are protean involving virtually every system of the body, with neurologic complications being one of the most severe, occurring in 25% or more of affected patients. [5 - 7] These neurologic complications include ischaemic and haemorrhagic strokes, transient ischaemic attacks, silent cerebral infarctions, seizures, headaches, and visual loss. [8 -,10] Stroke, resulting from cerebrovascular accidents (CVA), is devastating and potentially fatal. CVA could be overt typically due to large artery vasculopathy involving the intracranial parts of the internal carotid arteries and the proximal middle cerebral arteries or silent involving penetrating arteries of the major arteries. Approximately, 11% of SCA patients have a CVA before the age of 20 years, which is usually ischaemic.[11]

Thus, prevention is an important part of comprehensive care for children with SCD, especially those aged 2 to 16 years. It is routinely carried out in most developed countries with the use of Transcranial Doppler (TCD) ultrasonography; however, this facility is scarce in developing countries. In the 1990s, Robert Adams and associates demonstrated the efficacy and significance of TCD scanning in identifying children who were at a high risk of cerebrovascular accidents.[12] The Doppler scan evaluates the blood flow velocity of the brain's main arteries. The values obtained from this procedure are categorised as high (≥200cm/s), conditional (170 – 199cm/s) and normal or standard risk (< 170cm/s). Children with abnormal blood velocities are at high risk for CVA, while children whose velocities fall within the conditional range are at moderate risk for CVAs.

Considering that Transcranial Doppler ultrasonography has become routine in the management of children with SCA to prevent CVA and that some children may present with CVA even before their first TCD, this study aimed to describe the blood flow velocities of major arteries of the brain in children aged 2 to 16 years with SCA and classify their risk category. Additionally, the findings in this study will help advance understanding of this crucial clinical entity and add to the already existing knowledge on cerebral blood flow velocities.

Method

One hundred and two children with SCA between the ages of two and 16 years were enrolled in the study. The participants were recruited from the Paediatric Sickle Cell Clinic of Federal Teaching Hospital Owerri, Imo State, Nigeria. Ethical approval was obtained from the hospital's Research and Ethics Committee. Informed written consent and assent were obtained from the parents/caregivers and children aged 7 years and above, respectively, before enrolment in the study.

Inclusion criteria

Children aged 2 to 16 years were consecutively enrolled in the study during routine clinic visits. These include eligible children who were previously diagnosed with SCA as homozygous haemoglobin S disease using cellulose acetate electrophoresis at alkaline pH. All the children were in a steady state, defined as the absence of an acute illness (pain crisis, fever, or other SCA-related acute complications) or blood transfusion in the preceding four weeks.

Exclusion criteria

Children with acute illnesses such as fever, central nervous infection, major head injury, previous cerebrovascular accidents, epilepsy requiring anticonvulsants, and those receiving hydroxyurea were excluded from this study.

Data collection

Sociodemographic Data: A structured questionnaire obtained basic bio-demographic

data such as age, sex, and past medical, neurological and blood transfusion history.

Non-imaging TCD: All enrolled children' cerebral blood flow velocities were measured in line with the Stroke Prevention trial (STOP) in Sickle Cell Anaemia Disease protocol [13] using a 2-MHz hand-held probe connected to a Doppler box. The test measured and assessed the blood flow velocity in the anterior and middle cerebral arteries in the circle of Willis. When TCD hits a wave in the MCA (middle cerebral artery) and ACA (anterior cerebral artery) that can be heard and recorded, it produces audible noises. The procedure was performed utilising a non-imaging PMD Model 150 by Spencer Technology in Washington. During the procedure, the child laid on a bed and was conscious. A transducer was positioned directly on the child's temporal area (transtemporal window). The transducer was moved differently, so the ultrasound waves were directed towards the blood vessels under investigation. Several measurements were made for each vessel between 40 and 60 mm on both sides. The Time Averaged Mean Maximum Velocity (TAMMV) was used to capture the maximum velocity in the left and right cerebral arteries. Values greater than 170 cm/sec but less than 200 cm/sec were regarded as conditional risks, while a velocity of ≥200 cm/sec was regarded as abnormal (high risk). A TAMMV of less than 170 cm/sec was considered normal (standard risk). For this study, conditional and high risk were considered abnormal velocities, while the standard risk was considered normal. The average rise in any of the insonated vessels above 170cm/sec is said to be abnormal.

Data analysis

The data were collated and entered into the Excel spreadsheet. IBM Statistical Package for Social Sciences (SPSS) version 26.0 was used to analyse the data. Frequency tables were used to summarise TAMMV, age and gender distributions, and figures were utilised to summarise the patterns of CBFV. The data was subjected to normalcy testing and was normally distributed. Percentages and frequencies were generated for distributions of the CBF pattern. Differences in proportions between CBF pattern, age and gender were tested using the Chi-Square test. A p-value of <0.05 was considered statistically significant.

Results

A total of 102 children aged 2 - 16 years with SCA were studied. The mean age of the study participants was 7.7±4.4 years. Amongst the study participants, 55.9 % were males, while 44.1% were females. Most participants (60.8%) belonged to the middle socioeconomic class. The body weight ranged from 11kg to 90kg, with a mean of 28.0±14.7kg. The height also ranged from 0.72m to 1.78m with a mean of 1.3±0.2 m. The BMI of the participants ranged from 10.6kg/m^2 to 39.0kg/m^2, with a mean of 16.8±3.8 kg/m^2.

Table I: Sociodemographic and anthropometric characteristics of children with SCA

Variables		Frequency n (%)
Age group (years)		
	2- 6	46(45.1)
	7-11	31 (30.4)
	12-16	25 (24.5)
Gender		
	Males	57 (55.9)
	Females	45 (44.1)
Parent's social class		
	Lower	29 (28.4)
	Middle	62 (60.8)
	Upper	11 (10.8)
Nutritional Status		
	Underweight	17 (16.7)
	Normal	72 (70.6)
	Overweight	4 (3.9)
	Obese	9 (8.8)

TAMMV in the anterior and middle cerebral arteries

The time average mean maximum velocities ranged between 38.0 and 248.0 cm/sec. The minimum, maximum, and mean velocities and standard deviation in the RACA, LACA, RMCA and LMCA are shown in Table II. The lowest velocity was found in the left anterior cerebral artery, and the highest in the right anterior cerebral artery. The highest mean velocity was found in the left middle cerebral artery.

Pattern of cerebral blood flow

Most participants had a standard risk of 82.4%, while the prevalence of abnormal blood flow velocity (conditional and high risk) was 17.6% as shown in Figure 1.

Table II: TAMMV In the anterior and middle cerebral arteries in the study participants

	Minimum Velocities (cm/sec)	Maximum Velocities(cm/sec)	Mean Velocities(cm/sec)	Standard Deviation cm/sec
RACA	43.0	248.0	99.4	33.7
LACA	38.0	228.0	111.1	38.6
RMCA	41.0	242.0	116.4	37.1
LMCA	44.0	246.0	128.5	38.0

TAMMV – Time-Averaged Mean Maximum Velocity; RACA – Eight Anterior Cerebral Artery; LACA –Left Anterior Cerebral Artery; RMCA – Right Middle Cerebral Artery; LMCA – Left Middle Cerebral Artery

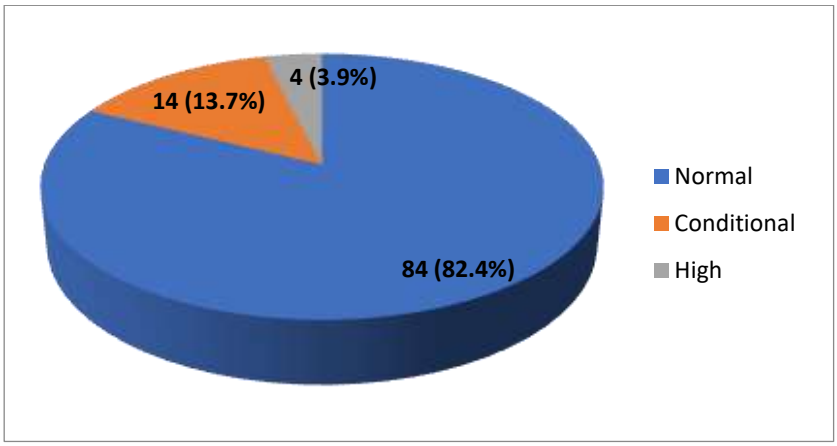

Figure I: Pattern of the cerebral blood flow velocities

Cerebral blood flow velocity pattern by age and gender

High-risk CBFV was seen in 3.9% (4/102) of the study population, and they were aged 2-6 years. The Conditional risk was seen in 14 of the 102 study participants. The prevalence of CR was 10.9% (5/46), 22.6% (7/31) and 8 % (2/25) in the children aged 2-6 years, 7-11 years and 12-16 years, respectively as shown in Table III. The majority of those with CR were aged 7 -11 years.

Relationship between Cerebral Blood Flow and Age

Ninety-two (23/25) of children aged 12 -16 years had normal velocities compared to the 80.4% (37/46) and 77.6% (24/31) seen in children aged 2-6 years and 7-11 years respectively. While abnormal flow was seen in only 8% compared to the 19.6% and 22.6% of those aged 12 -16 years, 2-6 years and 7-11 years respectively.

This difference was however not significant (χ^2 = 2.236 and p = 0.327).

Relationship between Cerebral Blood Flow and Gender

The blood flow pattern was similar in both males and females as shown in Table V

Table III: Cerebral blood flow velocity pattern distributed by age and gender

	Cerebral Blood Flow Pattern						
	Normal		Conditional		High		Total
Age (years)	Males n (%)	Females n (%)	Males n (%)	Females n (%)	Males n (%)	Females n (%)	
2 - 6	23 (50.0)	14 (30.5)	3 (6.5)	2 (4.3)	1 (2.2)	3 (6.5)	46
7 -11	13 (41.9)	11 (35.5)	5 (16.1)	2 (6.5)	0 (0.0)	0	31
12 - 16	11 (44.0)	12 (48.0)	1 (4.0)	1 (4.0)	0 (0.0)	0	25
Total	**47**	**37**	**9**	**5**	**1**	**3**	**102**

Table IV: Cerebral blood flow pattern distributed by age

Age in years	***Cerebral blood flow pattern***			***p-value***
	Normal n (%)	Abnormal n (%)	χ^2	
2-6 (n = 46)	37 (80.4)	9 (19.6)		
7-11 (n = 31)	24 (77.4)	7 (22.6)	2.236	0.327
12-16 (n = 25)	23 (92.0)	2 (8.0)		

Table V: Relationship between Cerebral Blood Flow and Gender

	Cerebral blood flow pattern			
Gender	Normal n (%)	Abnormal n (%)	χ^2	p-value
Male	47 (82.5)	10 (17.5)	0.000	0.975
Female	37 (82.2)	8 (17.8)		

Discussion

This was a hospital-based descriptive cross-sectional study. In this study, 102 SCA children aged two to sixteen years were recruited; 45.1% of study participants were 2-6 years with a mean age of 7.7 ± 4.4 years. The male-to-female ratio was 1.3:1. This is similar to that reported by Adekunle *et al.*,[14] and Lagunju *et al.* [15] who also studied ages two to sixteen years with a mean age of 7.66±4.2 years. Most of the study participants (60.8%) belonged to the middle socioeconomic class. This is similar to what Animasahun *et al.* [16] reported in Lagos. Conversely, Aliu *et al.* [17] in Gombe reported that 75.8% of their participants belonged to the low socioeconomic classes. Although all these studies were hospital-based, the findings documented by Aliu *et al.* may be explained by the location and degree of literacy.

In addition, anthropometric measurements showed an average weight of 28.0±14.7kg, an average height of 1.3±0.2m and an average Body Mass Index of 16.8±3.8kg/m^2. This is similar to the study by Odunvbun *et al.* [18] in Benin City, where the majority (86%) of children with SCA had normal height and weight. On the contrary, comparative studies of HbSS with their age and sex-matched HbAA controls by Ukoha *et al.* [19] in Enugu, Esezobor *et al*. [20] in Lagos, Fadhil *et al*. [21] in Egypt, Osei *et al.* [22] in Ghana all found a statistically significant difference in weight, height, BMI of SCA when compared with the controls. The difference between the previous and current studies may be explained by the fact that with better knowledge about the disorder, better nutrition and follow-up care, fewer children with SCA have poor growth indices.

This study assessed the CBFV of the vulnerable group for CVA in SCA (2-16 years). Ischaemic CVA due to SCA is uncommon before the age of two years, while the incidence diminishes after age 16 years.[11] Elevated levels of foetal haemoglobin offer protection in infancy, vasculopathy that results in infarction, and ischaemia develops over time and is thought to manifest as CVA from the third year of life. According to the STOP trial criteria, the TAMMV categorises SCA patients into three risk groups i) standard risk when the TAMMV in any of the insonated vessels is below 170cm/sec. This confers a 2% risk of CVA; ii) conditional risk when the CBFV is between 170 and 199cm/sec carrying 7% risk; iii) high risk is seen when TAMMV is 200cm/sec and above, conferring 40% risk for CVA.[13] In this study, the TAMMV ranged from 38.0 to 248.0 cm/sec. The highest velocity was recorded in the right anterior cerebral artery (RACA), followed by the left middle cerebral artery (LMCA). The lowest velocity was found in the left anterior cerebral artery (LACA). The middle cerebral and internal carotid arteries are the most valuable in evaluating CVA as they supply a significant portion of the cerebral hemisphere and are the common occlusion sites. The findings are in contrast to that documented by Lagunju *et al.*, [15] where the maximum velocity was recorded in a left middle cerebral artery (LMCA) followed by the left internal carotid artery (LICA), and the lowest velocity was recorded in the right and left anterior cerebral arteries. Furthermore, Adekunle *et al.* [14] and Ismail *et al.* [24] documented maximum velocity in the right MCA. However, while Adekunle *et al.* documented minimum velocity in the left ACA (similar to the current study), Ismail *et al.* documented minimum velocity in the left terminal internal carotid artery (different from the present study). The authors cannot explain the difference in the velocities found in the different arteries even though the same age group and methodology were studied.

Although most study subjects had standard-risk CBFV, similar to what was documented locally and internationally, [7,8,11,12,13] CBFV has been shown to change over time, so it is still imperative to continue annual screening and interventions for CVA in SCA because a significant proportion is still at risk of this life-threatening complication, where prevention is better than cure. The prevalence of abnormal CBFV documented in this study was 17.6%, of which 13.7% was conditional risk (CR) and 3.9% was high risk for CVA.

All the children with high-risk CBFV were aged 2-6 years, and the majority of those with CR were aged 7-11 years. The findings in this study showed that the prevalence of abnormal CBFV is higher in younger children than in older children. This is similar to the CVA prevalence of 4.0% reported from the Cooperative Study of Sickle Cell Disease (CSSCD).[11] In contrast, this study's prevalence of high-risk CVA is lower than previous reports of 7.8% and 11.5% from a

Jamaican and Dallas cohort study, respectively. [11,24] In Nigeria, the prevalence of high risk reported in this study is similar to 3% reported by Ismail *et al.* [22] in Kano but lower than reports of 5.4% by Ahmed *et al.* [25] in Abuja and Fatunde *et al.* [8] in Ibadan. Other higher local prevalence rated include 6.3%, 8.4%, 10.8% reported by Kehinde *et al* [26] in Lagos, Lagunju *et al.* [15] in Ibadan, and Adekunle *et al.* [14] in Lagos respectively. These differences may be related to the sample sizes of these studies.

The majority (92%) of participants with normal CBFV belonged to age 12-16 years, which is consistent with previous studies which reported a progressive decline in CBFV with advancing age. [13,14] All those with a high risk of CBFV were aged 2-6 years, which is suggestive that this age group should be given priority for screening in resource-poor settings. However, there was no association between CBFV and age. The current study showed that the majority (75%) of participants with high-risk CBF velocities were females, and 64.3% of those with CR were males. However, there was no association between CBFV and gender, similar to the study by Lagunju *et al.*[15] but different from the study by Chhadi *et al.* [27] in India, which reported a higher prevalence (70.6%) in males. This difference may be explained by the fact that the majority of the recruited study participants in the study by Chhadi *et al.* were males.

Conclusion

The prevalence of abnormal cerebral blood flow velocity among children with SCA in Owerri, Nigeria was high thus reiterating the role of CVA as an important debilitating neurological complication amongst children with SCA. Younger children are particularly at high risk of this complication. There is a need to increase the availability of transcranial Doppler ultrasound for routine screening of children with SCA. This will support early detection of children with SCA at risk of a CVA for prompt intervention that can avert the deadly complication.

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