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RELATIONSHIP BETWEEN CEREBRAL ARTERY BLOOD FLOW VELOCITIES AND SICKLE CELL SEVERITY

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ABSTRACT

INTRODUCTION

Sickle Cell Anaemia (SCA) is a chronic haemolytic state associated with recurrent blood transfusions, infections and its attendant complications. Vasocclusion results in the narrowing of the major cerebral blood vessel which predisposes children with SCA to the development of multisystem complications. Cerebral blood flow velocity can be assessed using transcranial Doppler ultrasound and the sickle cell disease severity can be assessed using scoring system by Adegoke and Kuti adopted for use in Nigeria for disease severity. The study compared the relationship between cerebral artery blood flow velocities (CBFV) and sickle cell disease severity in SCA children aged 2-16 years seen at Federal Teaching Hospital Owerri, Imo state.

METHODS

Sickle Cell Anaemia (SCA) is a chronic haemolytic state associated with recurrent blood transfusions, infections and its attendant complications. Vasocclusion results in the narrowing of the major cerebral blood vessel which predisposes children with SCA to the development of multisystem complications. Cerebral blood flow velocity can be assessed using transcranial Doppler ultrasound and the sickle cell disease severity can be assessed using scoring system by Adegoke and Kuti adopted for use in Nigeria for disease severity. he study compared the relationship between cerebral artery blood flow velocities (CBFV) and sickle cell disease severity in SCA children aged 2-16 years seen at Federal Teaching Hospital Owerri, Imo state.

RESULTS

A total of 102 subjects out of the 150 enrolled patients were screened within the study period. The values obtained from this procedure were categorized as abnormal (≥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. The prevalence of abnormal cerebral blood flow velocity of above 170cm/second was 17.6% (13.7% was at conditional risk zone and 3.9% at high risk zone). All the subjects at high risk zone were aged 2-6 years and 75% females. Ninety participants (88.2%) had mild disease while the remaining 12(11.8%) had moderately severe disease. None of the patients had a severe disease. Majority of those with mild disease had high risk for a CVA

CONCLUSION

The prevalence of abnormal cerebral blood flow velocity in SCA children is 17.6%. Identification of subjects at risk for a CVA although with a mild disease scores helped in primary prevention by prompt therapy institution.

KEYWORDS

Sickle cell anaemia, cerebral artery blood flow velocities, sickle cell disease severity

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INTRODUCTION

Sickle cell disease(SCD) is agenetic disorder resulting from a point mutation in beta globin, where hydrophilic glutamic acid is replaced by hydrophobicvaline.[1] With almost 305,000 live births affected, sickle cell disease 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; including Senegal, Madagascar, and malaria- endemic areas.[3] In Africa, 50-80% of infants born with SCD die before reaching five years because of increased risk of infections, inadequate erythropoiesis and increased risk of cerebrovascular accidents, according to cross-sectional surveys and cohort studies.[4]

Sickle cell anaemia (SCA) affects up to 2% of the global population, 90% of this global population reside in Nigeria, India and the Democratic Republic of Congo.[5] Twenty to thirty five percent of all SCD birth globally occur in Nigeria alone, and about 20 out of every 1000 live births have sickle cell anaemia according to World Health Organization (WHO) report[6].

Sickle cell anaemia (SCA) affects up to 2% of the global population, 90% of this global population reside in Nigeria, India and the Democratic Republic of Congo.[5] Twenty to thirty five percent of all SCD birth globally occur in Nigeria alone, and about 20 out of every 1000 live births have sickle cell anaemia according to World Health Organization (WHO) report[6].

Prevention of CVA is thus an important part of comprehensive care for sickle cell disease children especially those aged 2-16 years. This is routinely carried out in most developed countries through the use of Transcranial Doppler (TCD) ultrasonography although this service is not readily available in developing countries.

In the 1990s, Robert Adams and associates

demonstrated the efficacy and significance of TCD scanning by identifying children who were at a high risk of cerebrovascular accidents.[14] The Doppler scan evaluates the transcranial blood flow velocity in the main arteries of the brain. The values obtained from this procedure are categorized as abnormal (≥200cm/s), conditional (170 – 199cm/s) and normal (< 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.

SCA in children is known to exhibit great clinical diversity which can occur both between patients and even within the same individual. The spectrum ranges from persistent, severe and life threatening conditions associated with multiple organ dysfunction to mild and often asymptomatic disease with risk of late presentations and diagnosis.[15]

Adegoke and Kuti in 2013[15] introduced a scoring system to evaluate the clinical severity of SCA in Nigerian children using simple clinico-laboratory parameters which included frequency of crisis, hospital admissions and transfusions in the preceding one year, degree of liver and splenic enlargement, life- time cumulative frequency of specific complications of SCA, Packed cell volume and white blood cell count. The total scores ranged from 0-24 with less than 8 graded as mild, 8-17 moderate and more than 17 as severe disease. Genetic, environmental and geographical factors are the best recognized modifiers of disease severity.

Transcranial Doppler ultrasonography has become routine in the management of children with SCA and is readily available in developed countries. However, TCD is still scarce in developing countries like Nigeria and some children already had a CVA even before they get their first TCD ultrasound done therefore this study aimed at describing the blood flow velocities of major arteries in the brain of SCA children aged 2-16 years, to classify their risk category and determine the effect of disease severity on the CBFV.

METHODOLOGY

One hundred and two children with SCA between the ages of 2 and 16 were enrolled in the study. The participants were recruited from the paediatric sickle cell clinic of Federal Teaching Hospital Owerri, Imo state Nigeria. Approval was obtained from the hospital's Research Ethics Committee. Informed written consent and assent were obtained from the parents/caregivers before enrollment into the study.

Inclusion Criteria

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

Exclusion criteria

Patients with acute illness such as fever, central nervous infection, major head injury, previous cerebrovascular accidents, epilepsy requiring anticonvulsants were excluded from this study. Other exclusion criteria include children less than two years of age, those receiving hydroxyurea and recipients of chronic

blood transfusion, those with genotype Haemoglobin SC.

Data collection

Sociodemographic Data: A structured questionnaire was used to obtain basic bio-demographic data such as age, sex, past medical, neurological and blood transfusion history. Also severity criteria was obtained using Adegoke and Kuti severity scoring system.[15]

Non-imaging TCD: The cerebral blood flow velocities of all enrolled patients were measured in line with the Stroke Prevention in Sickle Cell Disease protocol using a 2-MHz hand-held probe connected to a Doppler box. The test measured and assessed the blood flow velocity in arteries, referred to as the Willis circle. When TCD hits a wave in the MCA and ACA that can be heard and recorded, it produces audible noises. The procedure was performed utilizing a non-imaging PMD model 150 by Spencer Technology in Washington.

During the procedure, the patient lay down on a bed and was conscious. A laptop computer was linked to a transducer, which gave the researcher information regarding blood flow. Using a tiny bit of gel, the transducer was positioned directly on the patient's temporal area (transtemporal window). The transducer was moved differently by the researcher so that the ultrasound waves were pointed towards the blood vessels under investigation. For each vessel, several measurements were made between 40 and 60 mm on both sides using the middle and anterior cerebral arteries. The TAMMV was used to capture the maximum velocity in the left and right middle cerebral arteries, as well as the left and right anterior 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 the purpose of analysis conditional risk and high risk were considered abnormal velocity while standard risk was considered as normal velocity.

Data Analysis: The data were entered into the Excel spreadsheet. For data analysis, the age was grouped into 3 cohorts (2–6 years, 7–11 years, and 12–16 years). IBM Statistical Package for Social Sciences (SPSS) version 23.0 was used to analyse the data. Frequency tables was used to summarise TAMMV, sickle cell disease severity by age and gender distributions and figures was utilised to summarise the patterns of CBFV. The data was subjected to normality testing and was normally distributed. Percentages and frequencies were generated for distributions of CBF pattern and sickle cell disease severity. Differences in proportions between CBF pattern, age and gender were tested using Chi square. A p-value of <0.05 was considered statistically significant.

RESULTS

Table I: Sociodemographic and Anthropometric characteristics of study participants

A total of 102 SCA children aged between 2 and 16 years old 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. Majority of the participants (60.8%) belonged to the middle socioeconomic class.

Table I: Sociodemographic and Anthropometric characteristics of study participants

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)

TAMMV in the anterior and middle cerebral arteries in the study participants

The time average mean maximum velocities ranged between 38.0 and 248.0 cm/sec. The minimum, maximum, mean velocities and standard deviation in the RACA, LACA, RMCA and LMCA are as 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.

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	111.0	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 –right anterior cerebral artery,
LACA –left anterior cerebral artery,
RMCA – right middle cerebral artery,
LMCA – left middle cerebral artery

Pattern of cerebral blood flow
Majority of the participants had standard risk with prevalence of 82.4%, while prevalence of 13.7% and 3.9% was found for conditional and high risk respectively. Conditional and high risk are abnormal (17.6%). See figure I

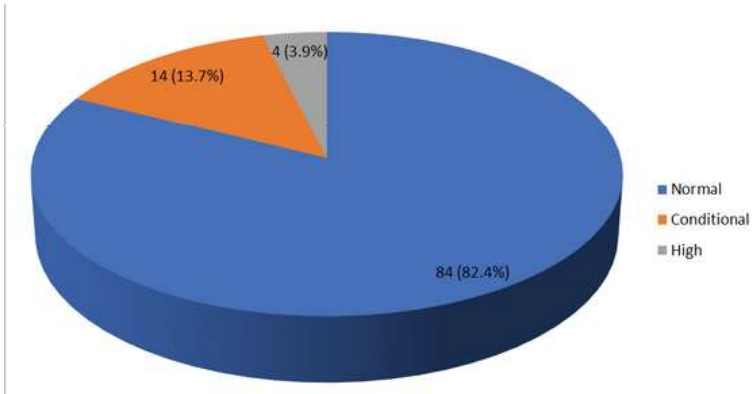

Figure I: Pattern of the cerebral blood flow velocities

Sickle Cell Disease Severity by Age and Gender
Ninety participants (88.2%) had mild disease while the remaining 12(11.8%) had moderately severe disease. Of the 90 with mild disease, 50(55.6%) were males and the rest were females. Their age groups are as shown in table III.

Table III: Sickle Cell Disease Severity by Age and Gender

SICKLE CELL DISEASE SEVERITY				
	Mild (N=90)		**Moderate (N=12)**	
Age in years	Male n(%)	Females n(%)	Males n(%)	Females n(%)
2 to 6	23(25.6)	17(18.9)	4(33.3)	2(16.7)
7 to 11	15(16.7)	11(12.2)	3 (25.0)	2(16.7)
12 to 16	12(13.3)	12(13.3)0	0(0)	1 (8.3)

Sickle cell disease severity and CBFV pattern
Majority of the participants had mild disease (88.2%).There was no relationship between sickle cell severity and abnormal CBFV ($\chi 2$ =0.009; p=0.924).

Table IV: Sickle cell disease severity and CBFV pattern

CBFV	Cerebral blood flow pattern		$\chi 2$	p value
	normal n (%)	Abnormal n(%)		
Mild	74(82.2)	16(17.8)	0.009	0.924
Moderate	10(83.3)	2(16.7)		

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 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[13] and Lagunju et al[14] who also studies ages two to sixteen years with mean age of 7.66 ± 4.2 years; M:F ratio was 1:1.4 and 9.22± 4.0 years; M:F 1.5:1 respectively. Majority of the study participants (60.8%) belonged to

to middle socioeconomic class. This is similar to that reported by Animasahun at al[16] in Lagos. Conversely, Aliu at al[17] in Gombe reported that 75.8% of their participants belonged to low socioeconomic class. Although all these studies were hospital based, the findings documented by Aliu et. al[17] may be explained by the location and degree of literacy.

This study assessed the CBFV of the vulnerable group for CVA in SCA (2-16years). Ischemic CVA due to SCA has been found to be uncommon before the age 2 while the incidence diminishes after age 16.[11] Elevated levels of fetal hemoglobin offers protection in infancy and vasculopthy that results in infarction and ischemia develops over time and is thought to manifest as CVA from the third year of life. According to the STOP trial criteria, the TAMMV is used to categorise 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 present study, majority of SCA patients had standard risk CBFV. This is the same as previously documented by different authors both within and outside the country.[13,14,16]This does not negate the fact that screening and interventions is important in the comprehensivemanagementofSCA patients. 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 are 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% out 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 majority of those with CR were aged 7-11 years. The prevalence of high risk CBFV in this study is similar to 4.0% reported from the Cooperative Study of Sickle Cell Disease (CSSCD).[13] In contrast however, the prevalence for high risk CVA in this study is lower than previous reports of 7.8% and 11.5% from a Jamaican and Dallas cohort study respectively.[13,16] This may be attributed to their genetic predisposition, iron deficiencies found which contribute to the risk of a CVA in them.

In Nigeria, the prevalence reported in this study is similar to the 3% reported by Ismail[17] in al[17] in Kano but lower than reports the 5.4% from Ahmed et. al[18] in Abuja and Fatunde et. al[10] in Ibadan; the 6.3%, 8.4%, 10.8% by Kehinde et. al[9] in Lagos; Lagunju et al[14] in Ibadan, Adekunle et. al[13] in Lagos respectively. In the present study, majority (88.2%) had mild disease, while 11.8% had moderate disease, no study participant had severe disease. This could be attributed to the fact that most of the haplotypes in Nigeria are of Benin type, which has intermediate levels of foetal haemoglobin and confers moderate disease severity.[15,20] In addition, patients with severe disease may have been excluded from the study possibly because they already had complications that required the use of hydroxyurea. Similarly, Adeodu et. al[21] in Ile-ife documented that majority (69.5%) had mild disease while 30.5% had moderate disease. On the other hand, Nnajekwu et al[22] in Enugu documented that majority (52%) of the study participants had moderate severity. This difference may be explained by the fact that Nnajekwu et. al[22] recruited SCA patients who already had complications and possibly more severe disease. Adegoke et al documented that 34% of their study participants had mild disease, 56% had moderate disease and 10% had severe disease.[15] Although, 75% of those with high risk CBFV and 92.9% with conditional risk CBFV had mild disease, there was no significant association between abnormal cerebral blood flow velocities and sickle cell disease severity. There is a dearth of literature on the relationship between severity of SCA and abnormal CBFV.

CONCLUSION

The prevalence of abnormal CBFV in SCA children aged 2-16 years in FUTHO was 17.6%. 88% of the participants had mild disease and 12% moderate disease. There was no relationship between abnormal CBFV and disease severity. Routine evaluation of disease severity in children with SCA will help to identify children at higher risk for a frequent clinical complication who may require close monitoring and management. There is need for regular TCD screening as those with mild disease can still have a CVA.

SOURCE OF FUNDING

Nil

CONFLICTS OF INTEREST

Nil

AUTHORS CONTRIBUTIONS

Ezeuko Lilian: conceptualization, study design, data analysis and interpretation, drafting of the manuscript, reviewing of the manuscript

Odunvbun Magdalene: study design, literature review, data interpretation, revision of the manuscript

Ikejiaku Udochikwuka: study design, literature review, data interpretation, revision of the manuscript

Ike Innocent: study design, literature review, data interpretation, revision of the manuscript

Onwumere Ugonna: study design, literature review, data interpretation, revision of the manuscript.

Ezeuko Vitalis: study design, data analysis, revision of manuscript

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SICKLE CELL DISEASE SEVERITY SCORES[15]

	0	**1**	**2**	**3**	**4**	**5**
No of pain episodes in the last 1 year	0	1	2-3	>3		
No of blood transfusions in the last 1 year	0	1	2-3	>3		
No of hospitalizations in the last 1 year	0	1	2-3	>3		
Liver enlargement	None	2-5cm	>5cm			
Splenic enlargement	<5cm	5-10cm	>10cm			
PCV **WBC**	>/=24% <11,000/mm	18-23% 11,000- <15,000/mm	<18% >15,000/mm			
complications	None	Gall stones, osteomyelitis, priapism and chronic leg ulcer	AVN	pcm	ACS	CVA