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Pattern of Cerebral Blood Flow Velocity Using Transcranial Doppler Ultrasonography in Children with Sickle Cell Disorder in Lagos State, Nigeria

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Abstract. Cerebrovascular accident (CVA) is a common, devastating neurological complication of sickle cell disorder (SCD) with a high recurrent and mortality rate. The Stroke Prevention Trial in Sickle Cell Anaemia study (STOP) recommends routine screening with transcranial Doppler ultrasonography in children aged two to sixteen years with SCD. The present study assessed cerebral blood flow velocities of children with SCD in accordance with the recommendation of routine screening by the STOP study.
Methods: **Transcranial Doppler ultrasonography was done for children with SCD that attended Sickle Cell Foundation, Nigeria between July and November 2015.**
Results: **In all, 388 subjects were screened within the study period (360 HbSS and 28 HbSC). The prevalence of abnormal Time-Averaged Maximum Mean Velocity (TAMMV) of at least 200cm/second was 10.8%: this was seen solely in HbSS subjects. The mean Time-averaged mean of the maximum (TAMM) velocity were 163±25cm/sec, 162±30cm/sec and 150±30cm/sec for children less than five years, five to ten years and eleven to sixteen years respectively.**
Conclusion**: The prevalence of abnormal TAMM velocity in children with HbSS is 10.8%. Identification of subjects at risk helped in primary CVA prevention by prompt therapy institution.**

Keywords: Transcranial Doppler Ultrasonography, Cerebrovascular Accident, Sickle Cell Disorder, Time-Averaged Maximum Mean Velocity.

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Introduction. Sickle cell disorder (SCD) is one of the commonest genetic diseases in the world. [1] Of the world's population, 5.2% carry a significant variant of sickle cell gene of which over 70% occur in sub-Saharan Africa.[2] Nigeria has the largest burden of sickle cell disorder in Africa with a prevalence of 3% in newborns.[2]

Cerebrovascular accident (CVA) is one of the most devastating complications of SCD that causes high morbidity and mortality in children; approximately 11% of children with SCD have a CVA before the age of twenty years[3] with a recurrence rate as high as 85% with the first three years of the first episode.[4] The reported prevalence of CVA in children with SCD in Nigeria varied between 4.3% and 6.8%,[5–7] the recurrence rate was as high as 61.5% in one of the studies.[6]

Children at risk of CVA can be identified using transcranial Doppler ultrasonography which enables evaluation of cerebral artery blood flow velocity with a sensitivity of ninety percent and specificity of one hundred percent when compared with cerebral angiography.[8] The Stroke Prevention Trial in Sickle Cell Anaemia study (STOP) recommends that yearly TCD screening should be done for children with SCD between the ages of two years and sixteen years with a repeat within three months for those children with abnormal results.[9] Following identified risk for a cerebrovascular accident in the anterior cerebral vessels in the extended STOP trial study,[10] the vessels were insonated.

Early identification of children at risk of CVA with cerebral blood flow velocity of at least 200cm/second and prompt interventions help to curtail the devastating neurological complication.[8]

Few studies have reported the prevalence of abnormal cerebral blood flow velocities in children in Nigeria. Lagunju et al.[11,12] in Ibadan, Nigeria in two studies reported 4.7% and 8.4% results of high risk for a CVA, 22.1% of the subjects had a conditional risk for a CVA. Oniyangi et al.[13] at Abuja, Nigeria reported that 6.9% of subjects had abnormal cerebral blood flow velocity and 81.4% had a normal study.

The present study aimed to determine the pattern of cerebral blood flow velocities of children with SCD that presents at Sickle Cell Foundation Centre, Nigeria within the studied period.

Materials and Methods. It was a cross-sectional study carried out at the Sickle Cell Foundation Centre, Idi -Araba Lagos between July and November 2015. It is a non-governmental organization that receives people with SCD all over the country. The foundation offers facilities like transcranial Doppler ultrasonography, genetic counseling, major diagnostic and research facilities and prenatal diagnosis of sickle cell disorder. The study population comprised children with sickle cell disorder aged two to sixteen years in a steady state that presented to Sickle Cell Foundation Centre. Steady state was defined as the absence of any crisis for at least four consecutive weeks with no history of blood transfusion in the previous four months prior to the screening. Children with previous CVA and on hydroxyurea were excluded from the study.

In all, 388 subjects were recruited with sample size calculation based on the previously reported prevalence of 8.4% by Lagunju et al.[11] Total sample size was divided into three age strata.130 subjects for the age group of less than five years, and 129 subjects each for the age group of five to ten years and eleven to sixteen years.

Approval for the present study was obtained from the Health Research Ethics Committee of Lagos State University Teaching Hospital.

The study was done using a Compumedics DWL Doppler machine (FDA K051 085) which is non-imaging. Recruited subjects TCD evaluations were done by one of the authors (M.O.) who had learned transcranial Doppler ultrasonography previously at the study center by a qualified trainer that does the transcranial Doppler ultrasonography at the center.

All recruited subjects had the Cerebral Blood Flow Velocities measured using a 2-MHz hand held probe attached to a Doppler box according to the Stroke Prevention in Sickle Cell Disease protocol.[9] The velocities of blood flow in the middle cerebral artery, internal carotid artery and anterior cerebral arteries were measured. The highest velocity in each artery was recorded as the Time-Averaged Maximum Mean Velocity (TAMMV). TAMMV less than 170 cm/second was considered normal, values greater or equal 170centimtre per second but less than 200 cm/second were conditional risks and velocity at least 200 cm/ second was considered abnormal. Further classification as low and high Conditional Risk according to TAMMV of 170 to 184cm/second and 185 to 199cm/second respectively was done.[9]

Results. Out of 388 subjects that had transcranial Doppler ultrasonography done, 360 were HbSS (92.8%), and 28 (7.2%) were HbSC. Their age range is two and sixteen years respectively while the mean age was 7.66±4.2 years. The female to male ratio is 1:1.4.

The minimum and maximum cerebral velocities were recorded in the left anterior cerebral velocity and right middle cerebral velocity respectively as shown in **table 1.**

The mean total TAMMV was highest in subjects below five years and lowest in subjects above ten years with a value of 161±26 and 149±31cm/sec respectively. Amongst the HbSS

Table 1.

Cerebral Blood Flow Velocities of Studied Subjects

Cerebral Arteries	Minimum CBFV (cm/seconds)	Maximum CBFV (cm/seconds)
Left ICA	39	252
Right ICA	46	232
Left MCA	52	276
Right MCA	49	307
Left ACA	25	224
Right ACA	32	222

Table 2. Mean Time-Average Maximum Mean Velocity according to age groups.

	Genotype		Total (Mean±SD)	T	p-value
	HbSS (Mean±SD)	HbSC (Mean±SD)			
Age group (years)					
< 5	163±25	130±25	161±26	3.128	0.002*
5-10	162±30	141±20	160±30	2.494	0.014*
11-16	150±30	121±12	149±31	5.898	0.009*

*Significant

subjects, the mean TAMMV of 163±25 cm/second was highest in under-5s. The mean TAMMV values were consistently higher in all the age strata in HbSS than in HbSC subjects.

In **Table 3**, the occurrence of abnormal TAAMV was seen only in HbSS subjects. The prevalence of abnormal cerebral blood flow velocity was 10.8%. Concerning HbSC subjects, all but one eight-year-old child had Conditional Cerebral Blood Flow Velocity.

For HbSS subjects, the frequency of normal Cerebral Blood Flow Velocity was highest in the 11 to 16-year-old age group (71.9%). The corresponding figures for younger age groups were 59.6% for under-5s and 59.1% for those between five and ten years. Thus, HbSS subjects in the 11 to 16-year-old age bracket had a higher frequency of normal Cerebral Blood Flow Velocity. Subjects within the age bracket of five and ten years had the highest prevalence of Abnormal Cerebral Blood Flow Velocity.

Conditional velocities were highest in subjects less than five years, intermediate in five to ten years and lowest in subjects eleven years a

Table 3. Risk levels of Cerebral Blood Flow Velocities result (TAMMV) of subjects based on hemoglobin variants.

TCD Risk group	Haemoglobin Genotype		p-value
	HbSS n=360(%)	HbSC n=28(%)	
Normal Risk	229 (63.6)	27 (96.4)	0.002*
Conditional Risk	92 (25.6)	1 (3.6)	
Abnormal Risk	39 (10.8)	0 (0.0)	
Mean ± SD	158 ± 29	134 ± 20	

SD = Standard Deviation; HbSS = Hemoglobin SS; HbSC = Hemoglobin SC; TCD = Ttanscranial Doppler

Table 4. Association between risk level of Cerebral Blood Flow Velocity and age group.

Hb genotype status	Age classification	TCD group			p-value
		Normal	Conditional	Abnormal	
HbSS	<5 years	74(59.6)	40(32.3)	10(8.1)	0.043*
	5-10 years	68(59.1)	32(27.8)	15(13.1)	
	11-16 years	87(71.9)	20(16.5)	14(11.6)	
HbSC	<5 years	6(100.0)	0(0.0)	0(0.0)	0.595
	5-10 years	13(92.9)	1(7.1)	0(0.0)	
	11-16 years	8(100.0)	0(0.0)	0(0.0)	

*Significant

above. Further classification of conditional velocities into high and low risk, eleven of the forty subjects in children below five years had a high conditional risk. The corresponding figure for five to ten years and eleven to sixteen years is five and three respectively.

Discussion. The prevalence of abnormal Cerebral Blood Flow Velocity among HbSS subjects in the present study was 10.8%. A similar prevalence of 10% was reported in a retrospective study in Philadelphia by Kwiatkowski et al.[14] Adam et al.[15] reported a similar prevalence of 9.7% in Georgia, USA. The prevalence of abnormal Cerebral Blood Flow Velocity in the current study is slightly higher than a prevalence of 8.4% in a Nigerian study by Lagunju et al.[11] In another Nigerian study by Oniyangi et al.,[13] a much lower prevalence of 6.98% Cerebral Blood Flow Velocity in children with SCD was reported. The higher prevalence in the index study compared to the survey by Oniyangi et al.[13] could be as a result of differences in methodology. While the current study used non-imaging TCD, the study by Oniyangi et al.[13] used imaging Doppler Ultrasonography. It has been demonstrated that TCD values from imaging studies are 10% to 15% lower than non-imaging ones.[16] No immediate explanation can be provided for the slightly higher prevalence of abnormal cerebral blood velocity in the present study compared with the reported value by Lagunju et al.[11] who also used a non-imaging Doppler machine. Studies have shown that about 95% of Nigerians with SCD have Benin haplotype and differences in haplotype will likely not explain the disparity. However, factors such as coexistence of alpha thalassemia as a likely factor is not routinely assessed in our environment, and it is beyond the scope of the current research.[17] The high prevalence of abnormal TAMMV in the present study underlines and supports the recommendation that transcranial Doppler ultrasonography should be done routinely. There have to be more efforts to make the Doppler machine more widely available. People travel from different regions of the country to have the screening done, and more children will benefit from routine screening if the services are closer to them. Prevention of a primary CVA in studied subjects was possible due to its early identification and therapy commencement. In our region, hydroxyurea is mostly adopted as a CVA preventive measures due to the cost of chronic blood transfusion and management of its possible complications as well as unavailability of blood products.[18]

The Stroke Prevention Trial in Sickle Cell Anaemia study (STOP) was carried out in African-American children with SCD. Values generated has been widely used in determining the risk for a CVA as applied in the present study. However, need for reassessment of cut-off values based on ethnicities and haplotypes has been suggested. So studies for re-evaluating race specific cut-off values for TAMMV are worthwhile.[19]

Younger subjects had a higher prevalence of abnormal Cerebral Blood Flow Velocity in the current study, similarly to the findings by Adam et al.[15] and Lagunju et al.[11] However, there were specific differences in the age ranges. Subjects aged five to ten years in the current study had the highest value of abnormal velocity compared to under 5s in the study by Lagunju et al.[11] and two peaks of two to nine years and nine to twelve years in the study by Adam et al.[15] However, the under-5 age group in the present study had the highest prevalence of high conditional risk. A possible explanation for the disparity in the age with the highest prevalence could be that while this study is cross-sectional, the study by Lagunju et al.[11] was a longitudinal study in which the subjects had serial TCD done over a two-year period. As noted by the authors, this allowed a number of the subjects with conditional risk to convert to abnormal risk. Also, the authors reported that the rate of conversion to abnormal risk was higher among subjects with high conditional risk than those with low conditional risk. In the current study, under-5were subjects have the highest prevalence of high conditional risk. Thus it can be suggested that if followed up with serial TCD this group is at significant risk of conversion to abnormal risk. Prevalence of CVA in SCD is commonest among children aged two to nine years, and this can account for the finding of high abnormal velocity in this age group compared to eleven years and above.

The mean value of Time-Averaged Maximum Mean Velocity was lower in HbSC subjects compared to HbSS subjects. In addition, none of the HbSC subjects had abnormal Cerebral Blood Flow Velocity. This datum is in keeping with reported lower TCD values and lower risk of CVA in HbSC people.[20] The explanation for the fact that none of the HbSC subjects had abnormal velocity

could be that hemoglobin SC disorder is associated with less severe hemolysis and the red cell life span is two times longer than HbSS. Thus they are less prone to hemolysis related vasculopathy and consequent abnormal TAMMV. Use of lower cut-off values of TAMMV have however been suggested in heterozygote children with SCD.[21,22] The occurrence of abnormal risk that was solely seen in HbSS subjects in the current study and others implies the need of prioritizing transcranial Doppler ultrasonography for HbSS subjects especially in regions like Nigeria where the machine and expertise are not readily available.

Conclusion. Prevalence of abnormal cerebral blood flow velocity is high in Nigeria children with SCA. There is a need for more availability of transcranial Doppler machine for routine screening of children with SCD. This will help in early identification of children at risk of a CVA for prompt intervention that can avert the deadly complication.

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