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Predictors of Cerebral Blood Flow Velocity in Children with Sickle Cell Anaemia in Lagos State, Nigeria

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Research Article

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ABSTRACT

The Stroke Prevention Trial in Sickle Cell Anaemia study (STOP) recommends routine screening with transcranial Doppler (TCD) ultrasonography in children aged two to sixteen years with SCA. However, in resource poor countries, unavailability of TCD machine limits the possibility of routine screening for all children with SCA. Readily available clinical and laboratory tools that can predict the risk of a CVA were assessed.

Methods: TCD ultrasonography was done for children with SCA that attended Sickle Cell Foundation, Nigeria between July and November 2015. Clinical and laboratory parameters were assessed as predictors of abnormal cerebral blood flow velocities.

Results: In all, 360 subjects were screened within the study period. Clinical predictors of abnormal Cerebral Blood Flow Velocity (CBFV) were elevated blood pressure and transcutaneous arterial oxygen saturation less than 95%. Significant haematologic correlates were low haematocrit, low haemoglobin concentration, leukocytosis, reticulocytosis and high Lactate dehydrogenase (LDH).

Conclusion: SCA children with low steady state haematocrit, low haemoglobin concentration, elevated blood pressure, leukocytosis, reticulocytosis and high LDH should be offered priority for TCD ultrasonography and institution of Preventive therapy for CVA.

INTRODUCTION

Cerebrovascular accident (CVA) is a major debilitating complication with a high risk of recurrence in children with sickle cell disorder [1]. In a Nigerian study, 12.4 per 1000 children with sickle cell anaemia (SCA) had CVA with a recurrence rate of 23.9% [2]. A higher recurrence rate of 61.5% has also been reported in children with SCD in Nigeria [3].

The risk of CVA is highest in children with SCA below ten years of age [4]. there is 80% risk of re-occurrence after the first episode [5]. The incidence of primary CVA in children with SCA has reduced in developed countries since the onset of routine transcranial Doppler ultrasonography and chronic blood transfusion therapy in those with a high risk of CVA [6].

Routine transcranial Doppler ultrasonography is recommended in children with sickle cell anaemia aged two to sixteen years with a repeat every six to twelve months [7].

Despite Nigeria having the highest children with SCD in the world, and also a high percentage of CVA, transcranial Doppler ultrasonography is not routinely done in all centers that care for children with the disorder due to non-availability of the machine and poor access to the few centers where the machine is available.

Clinical and laboratory predictors of elevated cerebral blood flow velocities are tools used in some region in the world to

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determine children at risk of a CVA. In Nigeria, there is paucity of data on clinical tools that can be used to predict CVA. Lagunju and co-researchers [8] identified young age, arterial oxygen saturation and low hematocrit as predictors of elevated cerebral blood flow velocity.

This study aim was to determine predictors of abnormal cerebral blood flow velocity using less expensive, more readily available screening tools like elevated blood pressure, complete blood count, low arterial oxygen saturation, high LDH and/or high urinary albumin/creatinine ratio if they are found to be sufficiently predictive.

The predictors of abnormal cerebral blood flow velocity can readily be used even in remote regions and resource poor countries and where there is no easy accessibility to transcranial Doppler ultrasonography in predicting those at risk of CVA for prompt intervention that can subsequently reduce the morbidity and mortality that can occur from the complication.

SUBJECTS AND METHODS

A prospective study carried out at Sickle Cell Foundation Centre in Lagos, Nigeria. This is a standardized non-governmental organization were transcranial Doppler ultrasonography is done for children that presents within Nigeria due to its highly subsidized price.

In all 360 children aged 2 to 16 years with sickle cell anaemia had transcranial Doppler ultrasonography done by one of the researchers (MO) who had training prior the commencement of the study.

Subjects were stratified according to age of below five years, five to ten years and above eleven years. There were 123 under 5 subjects, 115 and 122 subjects each in the age groups five to ten years and eleven to sixteen years respectively.

Sample size of 360 was determined using the previous publication on prevalence of abnormal cerebral blood flow velocity in Nigerian study by Lagunju et al. [8] of 8.4%.

Children whose caregiver gave a written consent and assent in those above seven years were recruited. Subjects were in steady state with no previous crisis in the last four weeks, no blood transfusion in the last 4 months, not on hydroxycarbamide and steroid.

Sitting blood pressure was taken using mercury sphygmomanometer with appropriate size cuffs three times after resting for nothing less than five minutes. The mean of the three readings was recorded as the blood pressure. Blood pressure percentile for all subjects was determined using the Centre for Disease Control percentile chart.

Transcutaneous oxygen saturation was done for all subjects in room air and values ≤ 95% was considered low.

Transcranial Doppler ultrasonography was done using a DWL Doppler non-imaging machine. All eligible children had the Cerebral Blood Flow Velocities measured using a 2-MHz hand held probe and measurement was done according to Stroke Prevention in Sickle Cell Disease protocol [8]. 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/s was considered normal, values greater or equal 170 cm/s but less than 200 cm/s were conditional risks and velocity at least 200 cm/s was considered abnormal. Further classification of conditional risk into low and high was done with TAMMV of 170 to 184 cm/s and 185 to 199 cm/s, respectively.

Collected data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20.0, a data analysis computer software programme. Patients' demographics were represented as frequency and percentages. Continuous variables were presented as mean ± standard deviation for parametric data. Normality of the parameters was tested using Kolmogorov-Smirnov test. Spearman correlation was used to test relationship between TAMMV and age and clinical parameters. Probability value less than 5% (0.05) was considered statistically significant.

RESULTS

The age range of subjects in the present study is two and sixteen years while the mean age was 7.66 ± 4.2 years. The female to male ratio is 1:1.3.

Table 1 below depicts the relationship between blood pressure percentile and TCD risk groups. For blood pressure less than 90th centile, the number of subjects decreased with increase in TAMMV.

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Table 1. Relationship between blood pressure percentile and TCD risk groups.

	< 50th	50-<90th	≥90-<95th	≥95-<99	≥99
	SYSTOLIC BLOOD PRESSURE PERCENTILE (%)				
TCD risk group					
Normal	191(74.6)	37(39.8)	0(0.0)	0(0.0)	0(0.0)
Conditional	58(22.7)	34(36.6)	1(14.3)	0(0.0)	0(0.0)
Abnormal	7(2.7)	22(23.7)	6(85.7)	4(100.0)	0(0.0)
	DIASTOLIC BLOOD PRESSURE PERCENTILE (%)				
TCD risk group					
Normal	188(74.3)	40(41.7)	0(0.0)	0(0.0)	0(0.0)
Conditional	55(21.7)	35(36.4)	2(28.6)	1(25.0)	0(0.0)
Abnormal	10(4.0)	21(21.9)	5(71.4)	3(75.0)	0(0.0)

Abbreviations: (%)=Percentage of subjects in each centile, TCD=Transcranial Doppler

Table 2. Relationship between Transcutaneous Oxygen Saturation and TCD Risk Status

SPO_2 Stratification	TCD group			p-value
	Normal	Conditional	Abnormal	
<95	43(54)	22(28)	14(18)	0.026
≥95	186(66.2)	70(24.6)	25(8.9)	

Abbreviations: TCD= Transcranial doppler; SPO2 = Transcutaneous oxygen saturation

Table 3. Variation of Mean Clinical and Laboratory Parameters in the Various TCD Risk Groups

Parameters	Normal	Conditional	Abnormal	p-value
	Risk	Risk	Risk	
MABP, mmHg	63.6 ± 7.2	66.1 ± 8.1	73.3 ± 9.6	0.0001*
SPO_2%	96 ± 8	96 ± 4	95.0± 3.5	0.001*
Haematocrit, %	25.1±3.4	23. 9 ± 3.2	22.3±3.0	0.0001*
HGB, %	8.3 ±1.1	8.0 ± 1.0	7.5 ± 1.0	0.0001*
RBC, 10^{12}/L	3.3 ± 0.7	3.4±2.8	2.8±0.4	0.152
MCV (fl)	77.2±8.8	77.7±7.3	79.0±6.6	0.404
MCH(pg)	26.2±5.9	26.0±2.8	26.8±2.8	0.737
MCHC(g/dl)	34.5±18.8	33.5±1.33	49.2±95.7	0.309
WBC, 10^9/L	12.7±5.5	15.9±12.4	15.2±7.5	0.002*
Platelet, 10^9/L	406.6 ±147.7	443±154.5	422.4±173.0	0.14
Reticulocyte, 10^9/L	10.57 ± 4.31	11.8±4.6	12.4±4.2	0.011*
LDH IU/L	652.4±178.5	739.0±101.3	728.8±97.9	0.008*
UACR mg/g	78±14.6	93±13.1	39.0±51.0	0.09

*Significant

Abbreviations: HBG= Haemoglobin Concentration; RBC= Red Blood Cell; WBC= White blood cell; UACR= Urinary Albumin Creatinine Ratio; LDH= lactate dehydrogenase; MCH= Mean Corpuscular Volume; MCH= Mean Corpuscular Haemoglobin; MCHC= Mean Corpuscular Haemoglobin Concentration.

Table 4. Correlation between TAMMV and Laboratory Parameters

Laboratory Parameters	Spearman coefficient	p Value
Haematocrit, %	-0.268	<0.0001*
HGB, %	-0.263	<0.0001*
RBC, 10^{12}/L	-0.27	<0.0001*
WBC, 10^9/L	0.291	<0.0001*
Platelet, 10^9/L	0.094	0.075
Reticulocyte, 10^9/L	0.2	<0.0001*
UACR, mg/g	0.092	0.082
LDH, IU/L	0.19	0.021*

*Significant

Abbreviations: HBG= Haemoglobin Concentration; RBC= Red Blood Cell Count; WBC= White blood Cell; UACR= Urinary Albumin Creatinine Ratio; LDH= Lactate Dehydrogenase

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Table 5. Multiple Linear Regression Analysis of Clinical and Laboratory Factors Contributing to Abnormal Cerebral Blood Flow Velocity in Subjects

	r^2	95%CI	P-value
Age	7.8	-0.103 to 0.098	0.0001*
MABP	5.2	0.319 to 0.427	0.0001*
SPO_2	2.9	0.163 to 0.185	0.942
Haematocrit	12.2	-0.103 to 0.098	<0.0001*
HGB	12.6	-0.295 to 0.017	<0.0001*
RBC	1.6	-0.124 to 1.219	0.899
WBC	3.7	-0.093 to 0.156	0.991
Platelet	1	-0.080 to 1.180	0.211
Reticulocyte	4.4	0.003 to 0.145	0.584
LDH	7.5	0.111 to 0.178	0.024*
UACR	1.8	0.012 to 0.123	0.123

Abbreviations: MABP= Mean Arterial Blood Pressure, WBC=White Blood Cell, RBC= Red Blood Cell, LDH= Lactate Dehydrogenase, HGB= Haemoglobin Concentration, UACR=Urinary Albumin Creatinine Ratio, r^2= Coefficient of Determination

DISCUSSION

Cerebrovascular accident is lethal but preventable complication in children with sickle cell disorder. Transcranial Doppler ultrasonography is recommended as a routine screening tool that identifies children at risk of CVA. In poor resource countries where transcranial Doppler machine is not readily available, the use of clinical and laboratory parameters that are likely predictors of abnormal cerebral blood flow will help in identifying those at a CVA risk for prompt institution of treatment. In the present studies clinical and laboratory parameters like blood pressure, transcutaneous oxygen saturation, complete blood count, lactate dehydrogenase, reticulocyte count and urinary albumin and creatinine ratio were assessed as likely predictors of abnormal cerebral blood flow in children with sickle cell disorder.

Elevated brachial arterial blood pressure was found to be a significant and independent predictor of abnormal Cerebral Blood Flow Velocity in the current study. This is similar to the findings in HbSS subjects studied by Colombattiet al. [9] The finding is not surprising because elevated blood pressure is a known risk factor for CVA [10,11]. The explanation for this is that chronic anaemia and abnormal rheological properties of sickled red cells can lead to cerebral vaso-occlusion which causes cerebral hypoxia. In order to maintain adequate cerebral oxygenation and cerebral perfusion pressure, there is compensatory increase in systemic blood pressure and Cerebral Blood Flow. Thus, relative hypertension may indicate decrease cerebral perfusion, cerebral ischaemia or cerebral vasculopathy which is detected by higher Cerebral Blood Flow Velocities [12].

The significant inverse relationship between oxygen saturation and Cerebral Blood Flow Velocities in this study is consistent with reports by other studies [8,13]. Cerebral hypoxaemia from haemoglobin desaturation leads to compensatory increase in Cerebral Blood Flow and Velocity. The physiologic basis is that SCD is associated with chronic cerebral hypoxia which induces release of adenosine and prostanoids which are potent cerebral vasodilators. This, in turn, increases Cerebral Blood Flow and Velocity [14].

Steady state haematocrit and haemoglobin concentrations were significant and independent negative correlates of abnormal Cerebral Blood Flow Velocity. Low steady state haematocrit and haemoglobin concentration as risk factors for abnormal Cerebral Blood Flow Velocity are the most consistently identified risk factors [8,13,15]. The physiologic explanation for this is that cardiac output and oxygen content of the blood determines oxygen delivery [16]. Hence, low haematocrit and low haemoglobin result in reduced oxygen delivery to the brain thus predisposing it to cerebral ischeamia and hence CVA. Also, chronic anaemia results in compensatory increased cardiac output, cerebral vasodilation which both results in increased Cerebral Blood Flow Velocity [17]. High Cerebral Blood Flow Velocity leads to damage of the intima, intima hyperplasia, progressive stenosis which can result in ischaemic CVA.

A significant positive correlation of Cerebral Blood Flow Velocity with leukocytosis was identified in the present study. This is similar to the findings by some researchers [9,15]. However, this is not a universal finding because Lagunju et al. [8] did not find leukocytosis as a predictor of abnormal Cerebral Blood Flow Velocity. It is difficult to explain the reason for this disparity. The explanation of leukocytosis causing increase in Cerebral Blood Flow Velocity is that leukocytes adhere to the vascular endothelium causing stenosis or occlusion of the cerebral vessels [18]. With vaso-occlusion, there is increase in the pressure of blood flow and hence, the velocity. This is the pathologic link between leukocytosis in the absence of infection being a risk factor for CVA [19].

Thrombocytosis was not a significant correlate of abnormal Cerebral Blood Flow Velocity in the current study. This finding is consistent with the study by Lagunju et al. [8]. There are paucity of data on thrombocytosis as a predictor of abnormal Cerebral Blood Flow. However, thrombocytosis, secondary to iron deficiency anaemia, as a risk factor for ischaemic CVA in SCD has been reported [20].

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A positive correlation between reticulocytosis and abnormal Cerebral Blood Flow Velocity was identified in this present study. This finding is consistent with report by Adams et al. [21] and Kwiatkowski et al. [22] study. Reticulocytes have adhesive properties that enhance the binding of sickled cells to the endothelium leading to endothelial damage and vaso-occlusion [23]. In cerebral vaso-occlusion, there is increase in the pressure of blood flow which is reflected by the high Cerebral Blood Flow Velocity [24].

High lactate dehydrogenase is a significant and independent predictor of abnormal Cerebral Blood Flow Velocity in this current study. This finding is consistent with other previous studies [25,26]. Lactate dehydrogenase is a marker of intravascular haemolysis. When intravascular haemolysis occurs, lactate dehydrogenase rises and in the presence of haemolysis and associated anaemia, there is increase in Cerebral Blood Flow and thus is a risk factor for the development of CVA [26].

Microalbuminuria is not a predictor of abnormal Cerebral Blood Flow Velocity in the present study, this is similar to the finding by Rees et al. [25]. However, in non SCD adults, albuminuria has been shown to be a risk factor for ischaemic CVA. Albuminuria was then suggested as a marker of endothelial damage with atherosclerotic process. The absence albuminuria as a risk factor for abnormal Cerebral Blood Flow Velocity in the current study and the study by Rees et al. [25] may suggest that albuminuria has no significant influence in its pathophysiology and the occurence of CVA.

Overall, clinical predictors of abnormal Cerebral Blood Flow Velocity were elevated blood pressure and transcutaneous arterial oxygen saturation less than 95%. Significant haematologic correlates were low haematocrit, low haemoglobin concentration, leukocytosis, reticulocytosis and high LDH. Of these significant correlates, the independent risk factors were mean arterial blood pressure, haematocrit, haemoglobin concentration and lactate dehydrogenase.

CONCLUSION

CVA is a fatal preventable complication in SCA. The unavailability of TCD ultrasonography in some centres in the developing countries including Nigeria makes prevention of CVA by identification of children at risk difficult. Use of readily available tools as predictors of abnormal TCD in these regions will be helpful in prompt recognition of children at risk for therapy institution.

AUTHORS CONTRIBUTION

Dr Adekunle, Dr Animasahun, Dr Akinwumi and Prof. Njokanma were involved in conception and design. Dr Adekunle and Prof. Njokanma were involved in acquisition of data. Dr Adekunle, Dr Akodu and Dr Ubuanne were involved in analysis and interpretation of data.

ETHICAL APPROVAL

Ethical approval was gotten from Health Research Ethics Committee of Lagos State University Teaching Hospital, Ikeja.

DECLARATION

On behalf of other co-authors, I hereby declare that this article is original and has not been submitted to any other journal for publication.

COMPETING INTEREST

No conflict of interest among the authors.

FINANCIAL DISCLOSURE

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