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Correlation of the middle cerebral artery blood flow velocity with age and Haemoglobin values of children with Sickle cell anaemia in Uyo

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Abstract

Introduction: Sickle cell anaemia (SCA) occurs in 1-3% of the Nigerian population. It is the most common cause of stroke in children. The time-averaged mean of the maximum velocity (TAMMV) in the Middle cerebral arteries (MCA) measured by transcranial Doppler (TCD) ultrasonography can estimate the risk of stroke in SCA children. Some clinical factors associated with abnormal TAMMV flows and first stroke (infarctive) in children with SCA are age and low haemoglobin.
Aim: To determine the association between TAMMV of the middle cerebral artery (MCA) in patients with SCA with their age and haemoglobin values and compare it with age and sex-matched children with Haemoglobin AA (HbAA) genotype.
Method: This was a comparative cross-sectional descriptive study conducted among 40 confirmed HbSS patients in steady state and a comparison group of 40 healthy HbAA age and sex-matched children. Demographic and medical data were obtained using a structured proforma. Haemoglobin concentration was estimated for all participants. TCD ultrasound was performed for all participants using the Stroke Prevention Trial in Sickle Cell Anaemia (STOP) protocol. Data was analysed in Statistical Package for Social Science version 22.0 (SPSS Inc., IL, USA).
Results: The mean and standard deviation (Mean±SD) age of HbSS patients was 9.1 ± 4.4 years. The majority (42.5%) of the HbSS children were in the 10-14 years age group. The HbSS patients had a consistently lower mean Hb than the HBAA participants across all age groups and this was statistically significant. (p=<0.001, <0.001, <0.001 and 0.001 respectively).
There was a significant difference in mean MCA velocity between HbSS and HbAA in the age groups above 5 years. (p <0.001). In addition, a significantly moderate positive correlation was observed between the Right MCA velocity and age in the HbSS population (r = 0.451, p = 0.004). While a significant negative correlation was observed between the measured TAMMV of the right MCA and the haemoglobin concentration in both the HbSS and HbAA groups (r = -0.490, p = 0.002) and (r = -0.600, p <0.001).
Conclusion: Our study has observed a positive correlation between age and MCA TAMMV and a negative correlation between Hb concentration and TAMMV in SCA children. The maintenance of adequate Hb in children with SCA is important in reducing the development of abnormal TAMMV velocities which carries a significant risk of stroke.

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artery.

Introduction

Sickle Cell Disease (SCD) is the most common haemoglobinopathy worldwide and includes disorders affecting the structure, function or production of haemoglobin).[1] Sickle cell anaemia (SCA) is the most common pathological haemoglobin variant worldwide. It affects 20–25 million people globally.[2] Over 75% of children with SCA live in Sub-Saharan Africa. The prevalence of SCA in Nigeria is 1-3%. Homozygous haemoglobin SS (HbSS) is associated with life-threatening morbidity and mortality of 50-80% before adulthood. The majority (70%) of these deaths are preventable with simple cost-effective primary preventive interventions.[3]

Sickle cell anaemia is the most common cause of childhood stroke. Stroke occurs in 5-10% of children with SCA before adulthood. The risk of stroke in children with sickle cell disease (SCD) can be assessed by measuring their cerebral blood flow velocities (CBFv). Cerebral blood velocity (CBV) in SCD can be measured non-invasively using Transcranial Doppler (TCD) ultrasound.[4] TCD has a sensitivity of 90% and a specificity of 100% in comparison to cerebral angiography in detecting significant abnormalities in intracranial arteries.[5] Blood flow velocity, measured using TCD is generally increased in severe anaemia in these patients, and it becomes elevated in a focal manner when stenosis reduces arterial diameter. Children with SCA who have a high risk of developing stroke can be detected with TCD ultrasonography months to years before the stroke.6 This early detection of risk enables the institution of primary preventive measures such as chronic transfusion regimens or the use of hydroxyurea. The Stroke Prevention Trial in Sickle Cell Anaemia (STOP) was the first stroke prevention trial in SCA and the first randomised, controlled multicentre trial designed to test whether reducing sickle haemoglobin to 30% or less with periodic blood transfusions will reduce first-time strokes by at least 70% compared to standard care. STOP screened more than 2000 sickle cell children using non-imaging TCD technique. STOP using non-imaging TCD, has categorised the risk of stroke in SCD into three using the measured CBV. The three categories are based on the time-averaged mean of the maximum velocity (TAMMV) in the middle cerebral or distal carotid artery; normal (<170cm/sec), conditional or borderline (170-199cm/sec), and abnormal TCD velocities (≥200 cm/sec).[7] Adams et al reported a 9.7% prevalence of abnormal TAMMV in HbSS children.[7] Lagunju et al and Adekunle et al using non-imaging TCDs have reported abnormal TAMMV prevalences of 8.4% and 10.8% respectively in Nigerian SCA children.[8,9] Some clinical factors are associated with the prevalence of abnormal TAMMV flows and first stroke (infarctive in nature) in children with SCA. Some of these factors include age, low haemoglobin, haemoglobin S genotype (HbSS), acute anaemic episode, recent acute chest syndrome, increased cerebral blood flow and cerebral vasculopathy.[10] Adekunle et al observed that children younger than five years old had the highest mean TAMMV.[9] Lagunju et al also observed a negative correlation between age and haematocrit level with TAMMV among HBSS children.[8,11] A Kenyan study also observed that a low haematocrit level was significantly associated with high CBFv.[12] The association of worsening anaemia with abnormal TAMMV is attributed to increased cerebral blood flow velocity.[13]

There is no published study on the association of age and haemoglobin level with TAMMV in children with SCA in our center. This study was therefore conducted to determine the association between the TAMMV of the middle cerebral artery (MCA) in patients with SCA with their age and haemoglobin values and compare it with age and sex-matched children with Haemoglobin AA (HbAA) genotype. Identification of the age and haemoglobin level that is associated with the highest TAMMV will aid clinicians and policymakers in identifying the target population that will benefit most from routine TCD measurements in a resource-constrained environment.

Methods

Study subjects and design

This was a comparative cross-sectional descriptive study conducted among 40 confirmed HbSS patients in steady state and a comparison group of 40 healthy Haemoglobin A genotype (HbAA) age and sex-matched children. The HbSS patients were aged 3-16 years in steady state. Steady-state was defined

as children who had been well without any signs of illness in the preceding four weeks and had not received any blood transfusion in the preceding four weeks.[14] Children with a previous history of stroke and those on hydroxyurea therapy were excluded. The comparison group were healthy children with the HbAA genotype. Children with abnormal haemoglobin concentrations were excluded.

Sample size calculation

The study size was calculated, using the formula: $n = Z^2 (p(1-p)/d^2)$,[15] with a known SCA prevalence rate of 1.5%.[16] A sample size of 40 subjects each for the study and control groups were recruited to account for attrition, giving a total of 80 subjects

Recruitment of study participants

The SCA children were consecutively recruited from the paediatric sickle cell clinic until the sample study size was achieved. The comparison group were recruited from the general paediatric outpatient clinic of the University of Uyo Teaching Hospital, Uyo, Nigeria. The exclusion criteria were a previous history of stroke in the SCA children and abnormal haemoglobin in the HbAA group. In addition, a lack of parental consent was an exclusion criterion in both groups. The study was conducted over five months. (June to October 2019).

Study tools

Demographic data (age and gender), current haemoglobin concentration and previous history of multiple blood transfusions were collected using a structured proforma. Two millilitres of blood was collected from each participant for confirmation of haemoglobin genotype and haemoglobin (Hb) concentration. Thereafter, TCD ultrasound was performed on the study participants by one of the authors (CA) who had been trained in the procedure using the STOP protocol.[13] The Ultrasound examination was performed with a high-resolution real-time grayscale and Doppler ultrasound scanner TOSHIBA NemioMX®, Model SSA-590A (Toshiba medical systems corporation, Japan 2011), using a sector transducer with a frequency of 2MHz. The grayscale scanning was done with the patient in the supine position. The patient's face was turned away from the region being scanned. Coupling gel was applied to the skin over the squamous tempora (just above the zygomatic arch) to obliterate the air interface between the probe and the skin. This trans-temporal approach was used via the posterior window which provided the best access to the intracranial circulation in most subjects. From this approach, the beam was directed anterosuperiorly and a large sample volume was employed.

For colour flow imaging, the transducer was placed on the temporal bone either above the zygomatic arch or anterior to the external auditory canal or slightly more posterior, above the earlobe. The ipsilateral MCA was colour-coded red denoting flow towards the transducer at a depth 40-65mm. The spectral flow also showed flow towards the transducer displayed above the zero baseline. The spectral wave tracing was done automatically by the machine or manually to obtain the TAMMV of the MCA, without angle correction or using a small Doppler angle close to zero (<60°) to the longitudinal axis of the vessel, for optimal spectral pattern. The pulse repetition frequency was set to avoid aliasing. Sampling was obtained from the right MCA and TAMMV obtained from the waveform tracing were recorded. At least three measurements were taken at varying depths on either side of the right MCA, between 40 and 65 mm. The highest recorded mean velocity for the artery was assumed to be the most representative and was recorded as the TAMMV.

Ethical considerations

Approval for the study was obtained from the Health Research Ethical Committee of the University of Uyo Teaching Hospital. Informed written consent was obtained from the parents/caregivers of younger subjects, while assent was obtained from older subjects before enlistment into the study. The data confidentiality was maintained by assigning study codes on data questionnaires instead of names and keeping a separate document that linked the study codes to subjects' names and other identifying information. This document was locked in a separate location and access to it was restricted. Security codes were also assigned to computerised records.

Data analysis

Data obtained from the questionnaire, the haemoglobin concentration and TCD sonographic

evaluation of subjects were analysed with the Statistical Package for Social Science version 22.0 (SPSS Inc., IL, USA). Continuous variables (age, haemoglobin and MCA velocity) were summarized as mean and standard deviation. Categorical variables (gender and age group) were summarised using simple frequencies and percentages. The differences in the mean of the continuous variables between the SCA patients and Controls were compared using the student T-test. Analysis of variance (ANOVA) was used to compare the continuous variables across the age groups. Categorical variables were compared using the Chi-square test or Fishers' exact test as appropriate. Pearson's correlation coefficient was used to correlate middle cerebral artery velocity with age and haemoglobin levels. The P value <0.05 was considered statistically significant. Data were presented in tables and correlation dot charts.

Results

The mean and standard deviation (Mean±SD) age of HbSSpatients was of 9.1 ± 4.4 years. The majority (42.5%) of the HbSS children were in the 10-14years age group There was no significant age or gender difference between the SCA and HbAA children (p= 0.952 and 1.000 respectively)

Haemoglobin distribution by age group in SCA patients

The mean ± SDhaemoglobin (Hb) concentration declined in the HbSS patients with increasing age and was lowest in the subjects ≥15 years (5.8 ± 0.5g/dl). This difference was however not statistically significant (p = 0.070). In contrast, the mean Hb concentration increased marginally with increasing age in the HbAA group and peaked at 10 – 14 years. This change was however not statistically significant (p = 0.656). (Table 2)

The HbSS patients had a consistently lower mean Hb than the HBAA participants across all age groups and this was statistically significant (p=<0.001, <0.001, <0.001 and 0.001 respectively) (table 3).

Right middle cerebral artery velocity distribution by age group

The right MCA TAMMV rose steadily with each age group in the HbSS population and the change in velocity across the group was statistically significant (p = 0.013). Among the HbAA group, the mean right MCA velocity did not vary significantly with each age group (p = 0.700). (Table 4)

There was no difference in the MCA velocity between HbSS and HbAA children below the age of five years. (0.151) However, there was a significant difference in mean MCA velocity between HbSS and HbAA in the age groups above 5 years. (p <0.001). (Table 5)

Correlations between right MCA velocity with age and haemoglobin concentration

There was a moderately positive correlation

Table 1: Sociodemographic distribution of the study population

	HbSS	HbAA	χ^2	P value
Age group	**No (%)**	**No (%)**		
<5	8 (20.0)	8 (20.0)		
5 – 9	11 (27.5)	13 (32.5)	0.340	0.952
10 – 14	17 (42.5)	16 (40.0)		
≥15	4 (10.0)	3 (7.5)		
Sex				
Male	23 (57.5)	23 (57.5)	0.000	1.000
Female	17 (42.5)	17 (42.5)		

Table 2: Haemoglobin distribution by age group

Group	Age group	n	Mean ± SD	Range	F value	*P value*
HbSS	<5	8	7.5 ±1.4	6.2 – 10.0		
	5 – 9	11	7.2 ± 1.3	5.8 – 10.2	2.566	*0.070*
	10 – 14	17	7.1 ±0.7	5.9 – 8.5		
	≥15	4	5.8 ± 0.5	5.1 – 6.3		
HbAA	<5	8	10.6 ± 0.9	9.7 – 11.8		
	5 – 9	11	11.1 ± 1.7	8.0 – 13.5	0.543	*0.656*
	10 – 14	17	11.3 ± 1.4	8.8 – 13.1		
	≥15	4	11.1 ± 1.4	9.4 – 12.2		

Table 3: Comparison of haemoglobin concentrations between HbSS and the controls

	HbSS		Controls			
Age group	N	Mean ± SD	N	Mean ± SD	t test	*P value*
<5	8	7.5 ±1.4	8	10.6 ± 0.9	-5.311	*<0.001*
5 – 9	11	7.2 ± 1.3	13	11.1 ± 1.7	-6.190	*<0.001*
10 – 14	17	7.1 ±0.7	16	11.3 ± 1.4	-10.690	*<0.001*
≥15	4	5.8 ± 0.5	4	11.1 ± 1.4	-6.674	*0.001*

Table 4: Right MCA velocity distribution by age group for HbSS patients and HbAA

Group	Age group	n	Mean ± SD	Range	F value	*P value*
HbSS	<5	8	75.0 ± 32.2	37.7 – 116.3		
	5 – 9	11	95.7 ± 18.8	54.7 – 121.9	4.125	*0.013*
	10 – 14	17	97.4 ± 15.4	58.6 – 118.0		
	≥15	4	120.9 ± 11.3	108.8 – 131.2		
HbAA	<5	8	57.3 ± 7.3	43.7- 68.6		
	5 – 9	11	54.1 ± 8.8	42.5 - 71.3	0.478	*0.700*
	10 – 14	17	55.4 ± 10.3	39.0 – 71.3		
	≥15	4	50.5 ± 0.9	49.5 – 51.2		

Table 5: Comparison of right MCA Doppler flow velocity distribution by age group between HbSS and HbAA subjects.

	HbSS		HbAA			
Age group	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**t-test**	***P value***
<5	8	75.0 ± 32.2	8	57.3 ± 7.3	1.518	*0.151*
5 – 9	11	95.7 ± 18.8	13	54.1 ± 8.8	7.064	*<0.001*
10 – 14	17	97.4 ± 15.4	16	55.4 ± 10.3	9.140	*<0.001*
≥15	4	120.9 ± 11.3	4	50.5 ± 0.9	10.752	*<0.001*

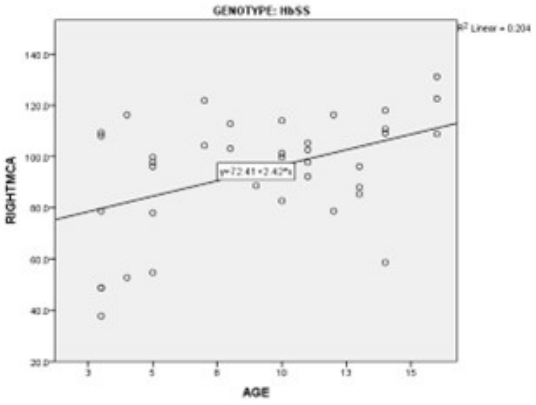

Figure 1: Linear regression scatter plot showing moderately positive correlation between right MCA TAMMV and age among SCA subjects

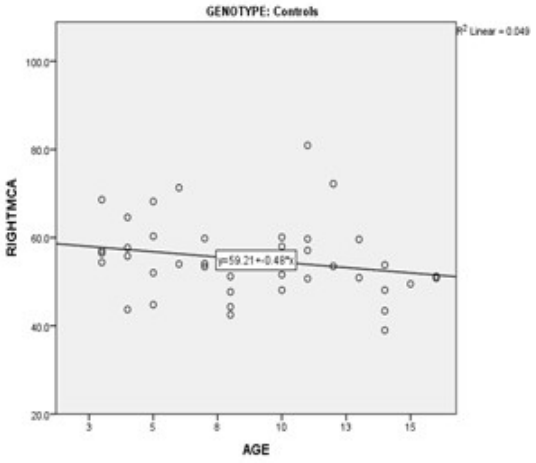

Figure 2: Linear regression scatter plot showing weak negative correlation between right MCA TAMMV

between the Right MCA velocity and age in the HbSS population (r = 0.451, p = 0.004). (Figure 1)

There is a moderately negative correlation between the measured TAMMV of the right MCA and the haemoglobin concentration in the HbSS group (r = -0.490, p = 0.002). (Figure 3)

There is a strong negative correlation between the measured TAMMV and haemoglobin concentration

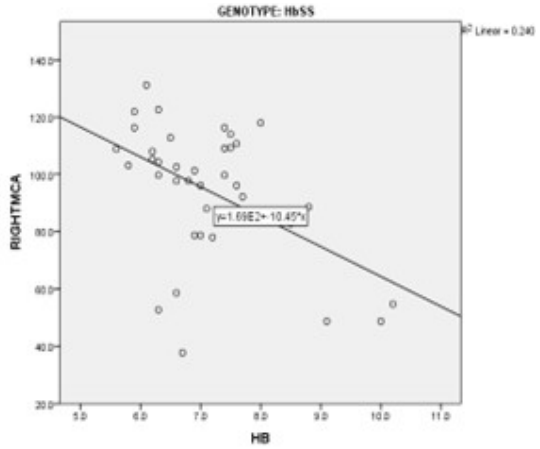

Figure 3: Linear regression scatter plot showing moderately negative correlation between Right MCA TAMMV and haemoglobin concentration among SCA subjects

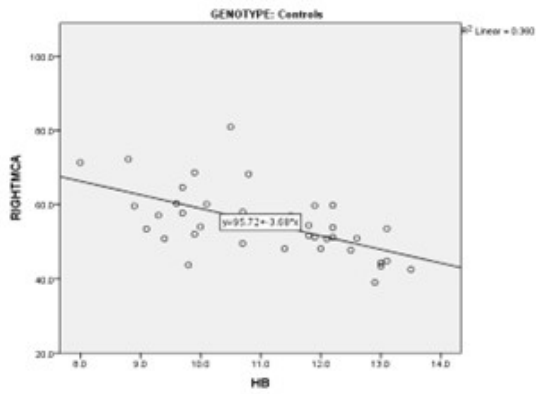

Figure 4: Linear regression scatter plot showing strong negative correlation between right MCA TAMMV and haemoglobin concentration among controls.

in the HBAA group. (r = -0.600, p <0.001). (Figure 4)

Discussion

Our study observed a steady decline in HB concentration in the HbSS group with age. In contrast, there was a steady increase in the Hb concentration across age groups of those with HBAA genotype. In addition, the Hb concentration of children with HbSS was significantly lower than those with HbAA genotype. These findings are expected because the chronic haemolytic state in SCA resulting from recurrent sickling and unsickling of the red cell leading to red cell

membrane damage keeps the patient in a permanent state of anaemia.[17]

All the children in the HbSS group belonged to the low-risk group (<170cm/s) as defined by the STOP study.[7] It should however be noted that stroke has been shown to occur in African children with subnormal TCD velocities <50cm/s. This underscores the need to consider other factors beyond increased cerebral blood flow and vasculopathy in the development of stroke in this group of children.[18] Lagunjuet al also speculated the possibility of African children developing stroke at a lower TCD level than American children.[8] The confirmation of this hypothesis will require long-term longitudinal cohort studies.

We observed a statistically significant (p = 0.013) increase in right MCA TAMMV with increasing age groups among the HBSS population. In contrast, there was a non-significant decrease (p=0.700) among the HbAA population with increasing age groups.

The finding of an increasing TAMVV among HbSS with age in our study could be explained by the chronic anaemia from chronic haemolysis leading to increased cerebral blood flow. This is corroborated by our observation of a decreasing Hb concentration with age among our HbSS population. In addition, cerebral vasculopathy leading to chronic cerebral artery stenosis could also explain this observation.[10] This observation is at variance with that of Ismail A. et al who found no significant difference in the TAMMV among different HbSS age groups.[19] Adekunle MO et al in Lagos, Nigeria observed that the older age groups recorded lower velocities. In their study, TAMMV among SCA subjects were 163±25 cm/sec, 162±30cm/sec and 150±30 cm/sec for children less than 5yrs, 5-10yrs and 11-16yrs respectively.[9] Differences in sample size may have contributed to the discrepancy between both studies.

Our finding of a decreasing TAMMV with age among children in the HbAA groups was consistent with the study by Adams et al who observed that cerebral blood velocities decreased with advancing age in non-anaemic normal children. The blood velocities were highest in young children (aged 4-8) and declined toward adult levels by age 16. Their study did not observe any added advantage of haematocrit to the prediction of MCA velocities after considering gender and age. They therefore concluded that in children without anaemia, knowledge of haematocrit levels had no added advantage to the interpretation of TCD.[20] The study by Schoning et al also corroborated this finding. However, our study population had lower MCA TAMMV compared to the study by Schoning et al which found higher mean values (93.2+13.0 [<10 years]vs83.2±11.9 [>10 years]).[21] The lower flow velocities in the MCA and ICA in older HbAA children have been attributed to the proportional growth of the cerebral arteries along with body development.[22]

In addition, HbSS children had significantly higher TAMMV (p=<0.001) than HbAA children in all age groups except for the <5 years group. Our observation of a statistically significant difference (p= 0.001) in TAMMV between the HbSS and HbAA groups in children > 5 years and the absence of a significant difference (p= 0.151) in children <5 years may be attributed to the presence of Fetal haemoglobin (HbF) in children <5 years. The persistence of HbF in SCA has been shown to reduce the sickling process and therefore offer additional protection and results in milder disease.[17] This protective effect of HbF has been shown by the reduction of the incidence of recurrent CVA in HbSS children receiving hydroxyurea.[23] In addition, cerebral vasculopathy develops over time and its effect may not be seen in younger children. It is also of note that none of our study participants had TAMMV >150cm/sec which has been associated with cerebral vasculopathy.[24]

Age had a moderately positive correlation (r = 0.451, p = 0.004) with TAMMV in the HbSS group. In contrast, Lagunju et al reported a negative correlation of TAMMV with age, with a decrease of about 0.2 cm/s for each monthly increase in age (95% CI= -0.34 to -0.04).(11)The discrepancy in our reports may be due to sample size differences and other methodological differences such as the longitudinal nature of the study by Lagunju et al compared to our study. Ismail et al did not find any significant correlation between age and TAMMV.[4] Adams et al recognised the importance of both age and haematocrit as potentially important variables in the interpretation of TCD examination in children. However, regression analysis did not indicate any advantage with the addition of age and

gender to haematocrit in the prediction of TAMMV.[25]

We observed a moderate negative correlation (r = -0.490, p = 0.002) of Hb concentration with TAMMV in the HbSS group and a strong negative correlation (r = -0.600, p <0.001) in the HbAA population. Our observation is similar to that of Lagunju et al who reported 1.8 cm/s decrease in TAMMV for every 1% increase in packed cell volume (95% CI= -2.73 to -0.81).[11] Ismail et al also reported a negative correlation of Hb concentration with TAMMV in Sudanese children.4 Adams et al reported a significant negative correlation between haematocrit with MCA velocity and they concluded that significant anaemia exerts a much more powerful effect than age in SCA patients without clinical stroke.[25] Reggiani et al in a longitudinal study reported a 7.243 cm/s decrease in MCA velocities for every 1g/dl increase in HB concentration in HbSS and sickle beta zero thalassemia (HbSβ0) genotypes. They also observed a reduction in imaging TCD (TCDi) abnormalities in children who had Hb concentration >9g/dl. They also observed an association between lower mean Hb (8.4g/dl) with conditional and abnormal TAMMV velocities.[26] These observations were not made in our study as we had no patients with conditional and abnormal TCD velocities.

The major limitation of our study was its small sample size. Other limitations included the operator dependency of ultrasonography and sound attenuation by the solid calvarial bone which affects the ultrasound findings. Serial studies would have yielded better results. To mitigate this at least three measurements were made per participant and the highest TAMMV was recorded. In addition, the occasional difficulty in getting acoustic windows, especially in dark older children could also affect the results. To mitigate this limitation, echo-enhancing contrast could have been used but it was not done in order not to cause undue pain to the children.

Conclusion

Our study has observed a positive correlation between age and MCA TAMMV and a negative correlation between Hb concentration and TAMMV in SCA children. We therefore recommend the maintenance of adequate Hb in children with SCA to reduce the development of abnormal TAMMV velocities which carries a significant risk of stroke.

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