


Cerebral artery conditional blood velocity in sickle cell disease: a multicentre study and evidence for active treatment

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ABSTRACT

Objective To obtain multicentre data on the prevalence of normal, high or conditional (intermediate) blood velocity in the cerebral arteries among children with sickle cell disease (SCD) in Nigeria.

Design A prospective observational study in five tertiary healthcare institutions. By transcranial Doppler (TCD) ultrasonography, cerebral artery peak systolic blood velocity (PSV) was determined in 193 children with SCD and time averaged mean of the maximum blood velocity (TAMMV) in a different cohort of 115 children. This design was to make the findings relevant to hospitals with TCD equipment that measure either PSV or TAMMV.

Setting Nigeria.

Participants 308 children (126 girls, 182 boys; age 2–16 years).

Main outcome measures Percentage of children with SCD who have normal, high or intermediate (often termed conditional) PSV or TAMMV.

Results In the cohort of 193 children, PSV was normal in 150 (77.7%), high in 7 (3.6%) and conditional in 36 (18.7%). In the cohort of 115 children, TAMMV was normal in 96 (84%), high in 7 (6%) and conditional in 12 (10%). There were no significant differences in gender or age distribution between the PSV and TAMMV cohorts. Altogether, cerebral artery blood velocity was normal in 246/308 children (80%), high in 14 (4.5%) and conditional in 48 (15.5%).

Conclusion Since conditional blood velocity in cerebral arteries can progress to high values and predispose to stroke, the proportion of children with SCD who are affected (15.5%) raises the question of whether regular monitoring and proactive intervention ought to be the standard of care.

INTRODUCTION

High blood velocity in the cerebral arteries of children who have sickle cell disease (SCD) is associated with increased risk of ischaemic stroke.^{1–9} Transcranial doppler (TCD) ultrasonography is used to determine the time averaged mean of the maximum blood velocity (TAMMV). Normal, high and intermediate (often termed conditional) values

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ In children with sickle cell disease, high blood flow velocity in the cerebral arteries is associated with an increased risk of stroke, and intermediate (often termed conditional) blood velocity in the cerebral arteries may progress to high values in a significant proportion of children with sickle cell disease.
- ⇒ Currently, there is no generally accepted standard of care for children with sickle cell disease and conditional cerebral artery blood flow velocity.
- ⇒ Single-centre studies of the percentage of children with sickle cell disease in Nigeria who have cerebral artery high or conditional blood flow velocity have yielded variable results.

WHAT THIS STUDY ADDS

- ⇒ This study provides multicentre data on the proportion of children with sickle cell disease in Nigeria who have conditional blood velocity in the cerebral arteries. These data are more likely to reflect the general situation in this country that has the highest birth rate of children with sickle cell disease.

of cerebral artery blood velocity in children with SCD had been established in previous studies^{4,9} and are used in routine clinical practice. The TAMMV in the internal carotid artery (ICA) or middle cerebral artery (MCA) is normal in a child with SCD if the highest value is <170 cm/s.^{4,9} A normal TAMMV in the ICA/MCA is associated with a clinically overt stroke risk of <1% per year in childhood SCD.^{4,9} The TAMMV in the ICA or MCA in a child with SCD is high if the highest value is >200 cm/s.^{4,9} A high TAMMV in the ICA/MCA is associated with a clinically overt stroke risk of 10% per year in childhood SCD.^{4,9} Highest TAMMV values in the ICA/MCA 170–199 cm/s in childhood SCD are described as intermediate or conditional because they might subsequently increase to abnormal values.^{4,9} Conditional TAMMV in the ICA/MCA is associated with



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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The findings from this study could guide the development of policies on standards of care for children with sickle cell disease and high and conditional blood velocity in the cerebral arteries.
- ⇒ Information from this study will enable paediatricians to have a more accurate picture of cerebral artery blood velocity. A more informed appreciation of this issue could prompt proactive intervention in clinical practice.
- ⇒ The results of this multicentre study of cerebral artery blood velocity in children living with sickle cell disease in Nigeria might serve as reference data for future nationwide epidemiological research.

a stroke risk of 3%–4% per year in childhood SCD.^{4–9} Some TCD machines determine peak systolic blood velocity (PSV) in the cerebral arteries.^{10–12} The normal PSV is <200 cm/s, high >250 cm/s and conditional 200–249 cm/s. The standard of care for high blood velocity in the ICA/MCA is regular blood transfusion to prevent stroke,^{1–9} but active intervention is not generally considered the standard treatment for conditional blood flow velocity. Conditional blood flow velocity does progress in a significant proportion of children to abnormal values that are associated with increased risk of ischaemic stroke.^{11–12} In a previous evaluation of the benefits of active intervention with 3 months of multimodal therapy comprising omega-3 fatty acids and potassium thiocyanate, progression of conditional blood velocity to abnormal values occurred in none (0%) of treated children relative to 14% of the control group on standard care of SCD only, and PSV reduced to normal values in 79% of the treatment compared with 43% of the control group.¹² Two other studies showed reduction of conditional blood velocity to normal values following hydroxycarbamide therapy.^{13–14} If a considerable percentage of children with SCD have conditional blood velocity in the cerebral arteries, proactive intervention with treatment modalities not associated with the hazards of regular blood transfusion or the potential cytotoxic side effects of hydroxycarbamide might be justifiable to reduce the number that progress to abnormal velocity.

In Nigeria, the country that has the largest population of people with SCD (3 million) and the highest SCD birth rate of 150 000 per year,^{15–18} previous studies of the percentage who have conditional blood velocity in the cerebral arteries have been in single healthcare institutions and yielded variable results.^{19–24} The objective of this study is to obtain multicentre data to represent the general situation in the country and so facilitate the development of policy on the care of children with SCD who have conditional blood velocity in the cerebral arteries.

MATERIALS AND METHODS**Study design and population**

Following approval by the Health Research Ethics Committee, informed consent by the legal guardians and assent by the children as appropriate, this prospective study was done in five tertiary healthcare institutions in Nigeria. The main outcome measure was the proportion of children with SCD who have normal, high or conditional PSV or TAMMV in the cerebral or internal carotid arteries. Although it was not possible to calculate the minimum sample size required for this study because the prevalence in Nigeria of cerebral artery conditional blood velocity in childhood SCD is not certain, a previous study in this

country recruited 232 children.¹² Guided by the previous report, the minimum sample size for this study was increased to 300. We studied 308 children with SCD (126 girls and 182 boys) aged 2–16 years. The haemoglobin phenotype had been confirmed by high performance liquid chromatography. In one cohort of 193 children with SCD (76 girls, 117 boys) cerebral artery PSV was determined by TCD. In another cohort of 115 children with SCD (50 girls, 65 boys), TAMMV in the cerebral arteries was determined. The design to determine PSV or TAMMV was deliberate to make the research findings useful to hospitals with TCD equipment that measure either parameter. Children with SCD who had stroke, or were on regular blood transfusion or hydroxycarbamide to prevent primary or secondary stroke, were excluded from this study. Sociodemographic data on the participants, including age and gender, were documented.

TCD ultrasonography

Trained personnel (two radiologists and one paediatrician) did the ultrasonography in all participants while in steady state SCD. To reduce interobserver variation,²⁵ ultrasonography was done following a written protocol. On each participant, two sessions of ultrasonography were performed, separated by a minimum interval of 30 min. This is to increase the reliability and reproducibility of the measurements at the specific time point. The average scan time was 15 min. Prior to the commencement of sonography, the procedure was explained to the participant and guardian. The participant was asked to lie in the supine position on a clinical examination couch and keep awake throughout the procedure. The sonographer sat comfortably on a chair near the head of the couch close to the TCD machine. The ultrasonic gel was applied to the 2 MHz transducer and placed at the temporal window (2–3 cm in front of the tragus of the ear). Adjustments were made to identify and optimise the spectral signals.

In accordance with current standards of care, children with high TAMMV or PSV in the anterior cerebral, middle cerebral or internal carotid artery were started on a blood transfusion programme to prevent ischaemic stroke. To determine PSV, TCD was done with a non-imaging (non-duplex) system: the Multigon Neurovision TOC 1M TCD system (Multigon Industries, Inc, Elmsford, NY, USA). The sample volume was 6–12 mm, the scale extended to more than 250 cm/s, acquisition commenced at 50 mm or near the bifurcation and peak velocities saved at an increment or decrement depth of 2 mm. Anatomical segments were identified by their depth, direction of flow, traceability, audio signal and spectral waveform. The anatomical segments of the MCA were primarily identified in this non-imaging TCD based on the distance from the bifurcation of the distal ICA. Ultrasonography was done on arteries of the left and right cerebral hemispheres. The highest PSV in the MCA, anterior cerebral artery or ICA were recorded. The distal ICA and its main branch the MCA were used in the study because most significant lesions occur in these arteries. The long linear tract of the MCA allows for ease of accessibility and reproducibility of the findings in a non-imaging study. For TAMMV, we used a non-imaging (non-duplex) system: the DWL Multidop T (DWL MDT 2419, Germany). The sample volume was 6 mm, the scale extended to more than 250 cm/s or as appropriate for the examination. Acquisition commenced at the distal MCA where signal is detected (≥ 30 mm) towards the bifurcation of the ICA, TAMMV saved at an incremental depth of 2 mm and terminated at the bifurcation of the ICA. Anatomical segments were identified by their depth, direction of flow, traceability, audio signal and spectral waveform. TAMMV for the distal ICA was recorded

from the bifurcation with angulation of the probe inferiorly. The highest value of TAMMV in the MCA or the distal ICA and the anatomical segment depth for each side were documented.

Those with normal PSV or TAMMV were reassured and booked for repeat TCD ultrasonography after 1 year. Children with conditional blood velocity were rescanned at 3-monthly intervals. In accordance with the standard of care, those with high velocity were started on regular blood transfusion to prevent stroke.¹⁻⁴

Statistical analysis

Data generated were collated and analysed with the Statistical Package for Social Sciences (SPSS V.23, IBM, Armonk, NY, USA). Frequencies, means and SD for demographic and ultrasound parameters were calculated. The two-tailed independent sample t-test was used to evaluate differences between parameters, and a p value of <0.05 taken as indicating a statistically significant difference.

RESULTS

A total of 308 children with SCD participated in this study: 126 girls and 182 boys. The age range for all participants was 2–16 years, the mean age was 8.86 years and the SD 3.98 years. Since two types of TCD machines are used in Nigeria,¹⁰⁻¹² PSV and TAMMV were measured in separate cohorts used to make the findings clinically relevant and useful to hospitals with either PSV or TAMMV equipment. The TAMMV cohort had 115 children (50 girls, 65 boys) with an age range of 3–16 years, mean±SD 8.78±3.37 years. The PSV cohort included 193 children (76 girls and 117 boys) with age range 2–16 years and mean±SD of 8.91±4.32 years. There was no statistically significant difference in age or gender distribution between the TAMMV and PSV cohorts (p>0.05). The proportions of children with normal, abnormal (high) or conditional (intermediate) blood velocity in each cohort is shown in table 1.

There was no difference in frequency of conditional velocity between the left and right cerebral hemispheres (table 2 and figures 1 and 2).

Supplementary data

Individual cerebral artery blood velocities in all the 308 children who participated in this study are accessible in online supplementary tables 1 and 2.

DISCUSSION

Stroke in a child adversely affects the life of the patient and that of an adult relative or guardian (usually the mother) who provides personal care for the child. In a child with SCD, stroke significantly increases the burden of care, the time and material resources expended and the adverse effects on family life; such

Table 1 Blood velocity in the cerebral arteries of children with sickle cell disease

Cohort	Normal	Abnormal (high)	Conditional (intermediate)
TAMMV n=115	96 (84%)	7 (6%)	12 (10%)
PSV n=193	150 (77.7%)	7 (3.6%)	36 (18.7%)
All participants n=308	246 (80%)	14 (4.5%)	48 (15.5%)

PSV, peak systolic velocity; TAMMV, time averaged mean of the maximum velocity.

Table 2 Comparison of blood velocity in arteries of the left vs right cerebral hemispheres

Blood velocity	TAMMV cohort n=115		PSV cohort n=193	
	Left cerebral hemisphere	Right cerebral hemisphere	Left cerebral hemisphere	Right cerebral hemisphere
Conditional (intermediate)	12	11	15	21
Abnormal (high)	5	3	1	6
Normal	98	101	177	166
Total	115	115	193	193

PSV, peak systolic blood velocity; TAMMV, time averaged mean of the maximum blood velocity.

as the inevitable reduction in attention paid by parents to the siblings of a child who has this haemoglobinopathy. So, stroke increases the psychological burden associated with SCD. Time devoted by the parents to care for their child who has a stroke usually translates to less time at work and loss of income to the family. By extension, this means a reduction in economic productivity, both nationally and globally. Medically, a cerebrovascular accident is a very serious complication that affects the outcome of SCD, especially if it recurs.^{1 2 12 18 26-29} Therefore, considered together, the medical, psychological, social and economic implications of stroke in a child with SCD are such that all care ought to be taken to prevent the accident in each individual at risk.

This multicentre study in five tertiary health centres in Nigeria found a prevalence of 15.5% for conditional (intermediate)

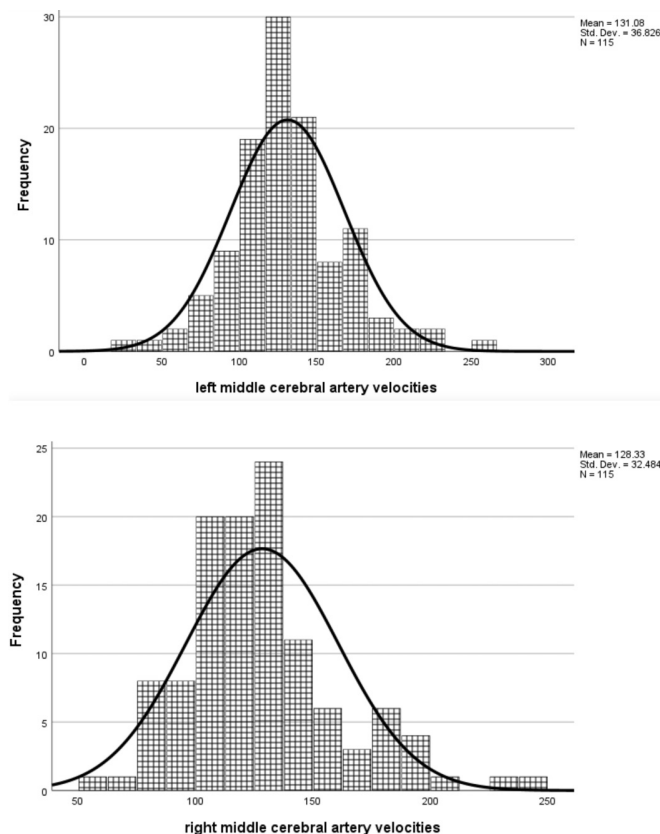


Figure 1 Frequency distribution of time averaged mean of the maximum blood velocity (cm/s) in the left (top) and right (bottom) middle cerebral arteries of children with sickle cell disease.

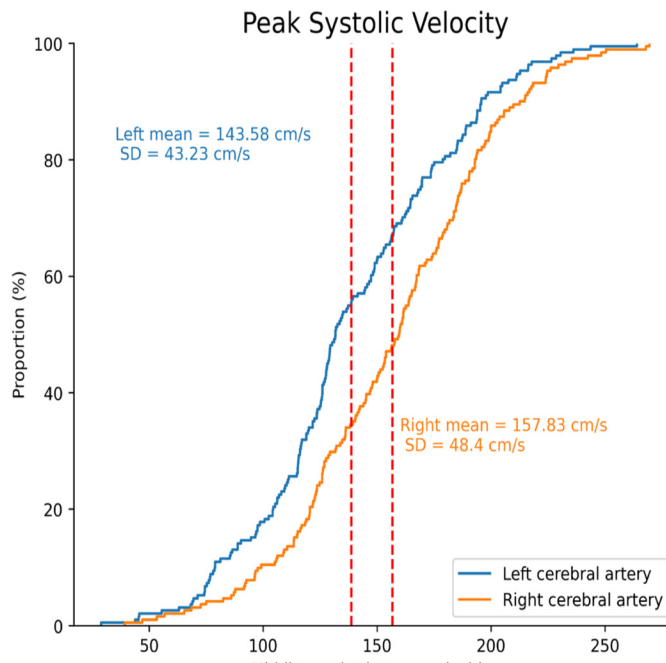


Figure 2 Cumulative frequency curves for peak systolic blood velocities (PSV, cm/s) in the middle cerebral arteries (MCAs) of children with sickle cell disease. Left MCA: curve to the left. Right MCA: curve to the right. Vertical dotted line to the left indicates mean PSV in left MCA; vertical dotted line to the right indicates mean PSV in right MCA.

blood velocity in at least one cerebral artery in children with SCD. This proportion differs from single-institution data of 25.6%²² and 21.9%²⁴ previously reported in Nigeria. Coexistent genetic factors in the study population, sample size, whether TAMMV or PSV was measured, and geographical spread of the participants might contribute to variation in the proportion of children with SCD who have conditional blood velocity in the cerebral arteries. A single-institution study in Nigeria showed that the coexistence of alpha thalassaemia trait protects against a rise in cerebral artery blood velocity, whereas no significant association with glucose-6-phosphate dehydrogenase was observed.²³ That the parameter used could affect the proportion with conditional velocity is suggested by the similarity in the percentage in the TAMMV cohort in this study (10%) and that of 9.9% from another multicentre survey of children with SCD in Brazil during which TAMMV was measured.³⁰

Children with conditional blood velocity can progress to abnormal (high) values that are associated with increased risk of stroke or cerebrovascular accident.^{12,13} In situations when thousands of individuals are at risk, the adverse effects of cerebrovascular accidents are multiplied accordingly. This is the situation in countries where thousands of children are born with SCD every year. For example, an estimated 150 000 children are born with SCD every year in Nigeria.^{15–18,31,32} Data from this study suggest that 15.5% of these could develop conditional blood velocity in at least one cerebral artery by the age of 16 years. This translates to an absolute number of over 20 000 children. Findings from a previous study of the benefits of proactive treatment of cerebral artery conditional blood velocity in SCD suggest that, untreated, this condition could progress to abnormal (high) velocity in 14% of affected Nigerian children.¹² The absolute number would be around 3000 children at increased risk of stroke. The same number would be added every year. So, the population of children with SCD and abnormal (high) blood velocity in cerebral

arteries would cumulate. Health service resources would be stretched to provide care for such a large population of children. In Brazil, 9.9% of children with SCD had conditional TAMMV.³⁰ Meta-analysis of data showed a 10.6% prevalence of conditional blood velocity across Africa.²⁶ Therefore, there is a strong case for active treatment of conditional blood velocity in SCD, and various studies have demonstrated its benefit.^{12–14}

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Contributors All authors contributed to data collection, drafting the manuscript, reviewing the revised drafts for accuracy and intellectual content, approved the final version of the manuscript as submitted and agree to be accountable for all aspects of the work. EM, BC and NI performed transcranial Doppler ultrasonography on the study participants. AM and CN-E carried out statistical analyses of the study data. IO conceptualised, designed the study and acted as guarantor.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Supplementary material: individual cerebral artery blood velocities in all the 308 children who participated in this study are accessible as online supplemental data in tables 3 and 4.

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