Received: 7 September 2023 | Revised: 9 October 2023 | Accepted: 16 October 2023

DOI: 10.1002/jha2.818

eJHaem

British Society for Haematology

RESEARCH ARTICLE

Transcranial Doppler ultrasound velocities in a population of unstudied African children with sickle cell anemia

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Funding information
National Institutes of Health Fogarty International Center, Grant/Award Number: 1R21HD106252-01

Abstract

The greatest burden of sickle cell anemia (SCA) globally occurs in sub-Saharan Africa, where significant morbidity and mortality occur secondary to SCA-induced vasculopathy and stroke. Transcranial Doppler ultrasound (TCD) can grade the severity of vasculopathy, with disease modifying therapy resulting in stroke reduction in high-risk children. However, TCD utilization for vasculopathy detection in African children with SCA remains understudied. The objective was to perform a prospective, observational study of TCD findings in a cohort of children with SCA from the Democratic Republic of the Congo, Zambia, and Malawi. A total of 770 children aged 2–17 years without prior stroke underwent screening TCD. A study was scored as low risk when the time-averaged maximum of the mean (TAMMX) in the middle cerebral artery or terminal internal carotid artery was <170 cm/s but >50 cm/s, conditional risk when 170–200 cm/s, and high risk when >200 cm/s. Low-risk studies were identified in

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604 children (78%), conditional risk in 129 children (17%), and high risk in three children (0.4%). Additionally, 34 (4%) were scored as having an unknown risk study (TAMMX <50 cm/s). Over the course of 15 months of follow-up, 17 children (2.2%) developed new neurologic symptoms (six with low-risk studies, seven with conditional risk, and four with unknown risk). African children with SCA in this cohort had a low rate of high-risk TCD screening results, even in those who developed new neurologic symptoms. Stroke in this population may be multifactorial with vasculopathy representing only one determinant. The development of a sensitive stroke prediction bundle incorporating relevant elements may help to guide preventative therapies in high-risk children.

KEYWORDS
Africa, sickle cell anemia, sickle cell disease, transcranial Doppler ultrasound

1 | INTRODUCTION

Sickle cell anemia (SCA) is the most common cause of childhood stroke worldwide [1]. In Africa, approximately 225,000 children with SCA are born each year [1, 2]. In affected children, repetitive vascular endothelial damage by sickled red blood cells results in cerebral vasculopathy and increased stroke risk. An estimated 60,000 children in Africa have life ending strokes related to SCA annually [1]. Physical impairments and neurocognitive dysfunction are common in survivors, negatively impacting quality of life for the child and family.

Targeted stroke prevention in SCA employs individual risk assessment by transcranial Doppler ultrasound (TCD). The degree of elevation of TCD flow velocities in the large cerebral arteries is a non-invasive marker of the presence and severity of cerebral vasculopathy. In the USA, a TCD examination is considered normal, with a low risk of primary stroke when the time-averaged maximum of the mean velocity (TAMMX) is <170 cm/s, conditional risk if 170–199 cm/s, and abnormal or high risk if ≥200 cm/s [3–6]. Initiating chronic, monthly blood transfusions in children with a high-risk TCD reduces stroke incidence by 92% [7]. Hydroxyurea is an alternative therapy that is as efficacious at reducing TCD velocities and primary stroke in children with SCA, including those living in Africa [8–12]. TCD is emerging as a screening tool for sickle cell-associated vasculopathy on the continent, but significant knowledge gaps around interpretation of results in this context remain. We therefore performed this prospective, observational study and report on initial TCD screening results in a large cohort of African children with SCA.

2 | METHODS

Six TCD Centers of Excellence (COE) in sub-Saharan Africa (SSA) were formed to enhance the utilization of TCD in pediatric patients in Africa (1R21HD106252). This was a prospective, observational study performed at these centers, including: (1) Kinshasa, Democratic Republic of the Congo (DRC), (2) Lodja, DRC, (3) Bunia, DRC, (4) Lusaka, Zambia, (5) Chipata, Zambia, and (6) Blantyre, Malawi from September 2021 to February 2023. Ethics approval was obtained in each country (DRC CES ID 279/CNES/BN/PMMF/2021, Zambia ERES ID 00005948, Malawi COMREC waived need for consent and incited standard of care). When needed, guardians gave informed consent prior to participation.

Children 2–17 years of age with SCA at each TCD COE were eligible to participate. Following enrollment, children underwent confirmation of hemoglobin SS disease. If medical records documented a previous hemoglobin electrophoresis, this was considered acceptable. If not, confirmatory testing using Sickle SCAN (Biomedomics) was undertaken. Sickle SCAN is a multiplexed, qualitative, point-of-care immunoassay that has excellent sensitivity (94%–99%) and specificity (100%) in the diagnosis of SCA in the African setting [13]. Patient demographic and vital signs were measured. Given the potential impact of anemia on measured TCD flow velocities, hemoglobin values at the time of each TCD examination were determined using point-of-care testing (HemoCue).

Each participant underwent TCD examination. TCD studies were performed by individuals who had successfully completed the SSA TCD Academy course content which includes: (1) 12 online didactic lectures designed to teach basic concepts of TCD science including neuroanatomy, scan techniques, Doppler waveform characteristics, diagnostic criteria, and clinical applications in children, (2) 100 case studies aimed to develop interpretation skills, (3) a hands-on introduction to TCD training session to develop TCD scanning proficiency where >50 proctored studies were performed, and (4) a written examination. The course was considered successfully finished when didactics and case studies were reviewed, the participant demonstrated proficiency in TCD scanning (each measurement of three different complete TCD examinations had a coefficient of variation <10% from that of the trainer [N.O.], and the written examination was passed). TCDs were acquired at each site using a commercially available TCD device (Lucid TCD, NovaSignal).

The TAMMX cerebral blood flow velocity (CBFV) was determined in the bilateral middle cerebral arteries (MCA) at three points and in the bilateral terminal internal carotid arteries (tICA) at two points in 2 mm intervals. Studies were exported from the machine onto a USB and uploaded to an encrypted, secure database for central interpretation (by N.O.). The reader placed each study into one of five mutually exclusive categories (low risk, conditional risk, high risk, unknown risk, or inadequate) using the following definitions:

1. Low risk = highest TAMMX velocity in both MCAs and tICAs <170 cm/s but >50 cm/s
2. Conditional risk = highest TAMMX velocity ≥170 but <200 cm/s
3. High risk = highest TAMMX velocity ≥200 cm/s
4. Unknown risk = lowest TAMMX velocity ≤50 cm/s
5. Inadequate = studies lack sufficient data for classification

All participants families were questioned on initial screening to determine if their child had previously suffered a clinically apparent cerebral infarction utilizing the World Health Organization (WHO) definition: rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 h or longer with no apparent cause other than of vascular origin [14]. Baseline neurologic assessments were also performed at enrollment to identify gross neurologic deficits indicative of likely past stroke. Children with a previous history of stroke with ongoing evidence of gross neurologic deficits were excluded from the study. Prospective stroke determination was carried out by study staff that ensured that the WHO definition was met and that neurologic deficits were evident on clinical examination.

2.1 | Statistical analysis

Descriptive values were expressed as frequencies and percentages for dichotomous variables and as mean ± SD for normally distributed or median (interquartile range) for non-normally distributed continuous variables. For comparisons between proportions, chi-squared tests were used. For comparison of continuous variables, independent sample *t*-test was used. Linear regression was used to explore associations between TAMMx and age and hemoglobin given the possible association with these factors and measured flow velocities [15, 16]. All analyses were completed with GraphPad (version 9.0). A $p < 0.05$ was considered statistically significant.

3 | RESULTS

A total of 872 patients underwent study consent and screening. Five patients were found not to have hemoglobin SS disease. An additional 48 (6.1%) had an inadequate TCD, largely due to lack of insonation window ($n = 26$, 3.3% of the total population with hemoglobin SS disease, mean age of 12.2 ± 2 years) or lack of cooperation by the patient ($n = 20$, 2.5% of the total population with hemoglobin SS disease, mean age 2.1 ± 0.5 years). Two patients had an incomplete study, but reasons for failure were not documented. Forty-nine patients were excluded based on previous history consistent with stroke. Seven hundred and seventy patients were included. Demographics, hemoglobin values, and TCD examination results for the cohort are available in Table 1. Of 770 scans in children with SCA, MCA mean flow velocities were: 105 ± 29 cm/s for children 2–3.9 years of age, 109 ± 27 cm/s for children 4–6.9 years of age, 105 ± 24 cm/s for children 7–9.9 years of age, and 93 ± 26 cm/s for children ≥10 years of age. A total of 604 (78%) were graded as low risk, 129 (17%) as conditional risk, three (0.4%) as high risk, and 34 (4.4%) as unknown risk (Table 1). Age of participants by risk stratification is also available in Table 1. Age was not significantly associated with mean flow velocity (−0.45, 95%

TABLE 1 Demographics, laboratory investigations, and transcranial Doppler ultrasound (TCD) examination results for children with sickle cell anemia.

Variable	No stroke history ($n = 770$)
Demographics	
Age (years), mean (SD)	7.3 (±4.3)
Age (years) at time of diagnosis of SCA, mean (SD)	2.9 (±2)
Number of previous transfusions, median [IQR]	2 [0, 3]
Taking hydroxyurea, *n* (%)	139 (18%)
Laboratory investigations	
Hemoglobin (g/dL), mean (SD)	7.5 (±1.7)
TCD risk classification	
Low risk, *n* (%)	604 (78%)
Conditional risk, *n* (%)	129 (17%)
2–3.9 years old	46 (36%)
4–6.9 years old	62 (48%)
7–9.9 years old	11 (8%)
>10 years old	10 (8%)
High risk, *n* (%)	3 (<1%)
2–3.9 years old	1 (33%)
4–6.9 years old	1 (33%)
7–9.9 years old	1 (33%)
Unknown risk (mean flow <50 cm/s), *n* (%)	34 (4%)
2–3.9 years old	8 (24%)
4–6.9 years old	6 (18%)
7–9.9 years old	5 (15%)
>10 years old	15 (44%)
Other TCD parameters	
Right to left MCA variability (%), mean (SD)	18.7 (±20)
Pulsatility index, mean (SD)	0.83 (±0.08)

Abbreviations: IQR, interquartile range; MCA, middle cerebral artery; *n*, number; SCA, sickle cell anemia; SD, standard deviations.

TABLE 2 Comparison of transcranial Doppler ultrasound (TCD) examination results in children aged 2–16 years of age with sickle cell anemia in the USA to TCD examination results in children aged 2–17 years with sickle cell anemia in sub-Saharan Africa.

	TAMMX subnormal (MCA/ICA <50 cm/s)	TAMMX normal (MCA/ICA <170 cm/s)	TAMMX conditional (MCA/ICA 170–199 cm/s)	TAMMX abnormal (MCA/ICA ≥200 cm/s)
USA				
Adams et al. ($n = 315$)	N/A	260 (83%)	30 (9%)	25 (8%)
Nigeria				
Lagunju et al. (2012) ($n = 145$)	N/A	110 (76%)	29 (20%)	6 (4%)
Soyebi et al. (2014) ($n = 2300$)	N/A	1640 (71.3%)	444 (19.3%)	216 (9.4%)
Prussien et al. (2019) ($n = 83$)	N/A	70 (84%)	7 (9%)	6 (7.2%)
Modebe et al. (2023) ($n = 115$)		96 (84%)	12 (10%)	7 (6%)
Kenya				
Makani et al. (2009) ($n = 105$)	7 (7%)	95 (90%)	3 (3%)	0 (0%)
Tanzania				
Kija et al. (2020) ($n = 200$)	39 (19%)	149 (75%)	11 (5.5%)	1 (0.5%)
Ambrose et al. (2020) ($n = 202$)	N/A	154 (77%)	42 (21%)	4 (2%)
Sudan				
Ismael et al. (2019) ($n = 119$)	24 (20%)	95 (80%)	0 (0%)	0 (0%)
Uganda				
Green et al. (2019) ($n = 251$)	0 (0%)	208 (82%)	38 (16%)	5 (2%)
DRC, Zambia, Malawi				
O'Brien et al. (current) ($n = 770$)	34 (4.6%)	604 (78%)	129 (17%)	3 (0.4%)

Abbreviations: DRC, Democratic Republic of the Congo; ICA, internal carotid artery; MCA, middle cerebral artery; *n*, number; N/A, not applicable; TAMMX, time-averaged maximum of the mean.

confidence interval [CI] −0.99 to 0.09, $p = 0.1$). Hemoglobin was significantly negatively associated with mean flow velocity (−3.4, 95% CI −4.9 to −1.9, $p < 0.001$).

A comparison of screening TCD results between the original pediatric SCA work done in the USA by Adams et al. and the results of other studies in African children with SCA and our cohort is shown in Table 2. Over the course of 15 months of follow-up, 17 (2.2%) children with no previous stroke history developed a primary stroke. Six had a low-risk TCD screening result, seven had a conditional risk, and four had an unknown risk. A comparison of stroke incidence between the original pediatric SCA work done in the USA by Adams et al. and the results of other African studies that report prospective stroke risk based on TCD classification and to our cohort is shown in Table 3. The mean follow-up period where stroke incidence was evaluated was significantly different between studies, with those children in the USA being followed for 64 months versus 36 months in Kenya and only 15 months in the current study ($p < 0.001$).

4 | DISCUSSION

More than 75% of the global burden of SCA occurs in SSA, where an estimated 1.03 million children are afflicted. Scarce health resources contribute to high early mortality rates: an estimated 50%—90% of infants born with SCA in Africa die before their fifth birthday. In 2018, a meta-analysis determined that approximately 60,000 children with SCA have ischemic strokes annually on the continent, contributing to this high mortality rate [1]. Identifying children at high risk of stroke that would most benefit from disease modifying therapies such as hydroxyurea may improve outcomes of African children with SCA. TCD is emerging as a screening tool for sickle cell-associated vasculopathy on the continent, but significant knowledge gaps around interpretation of results in this context remain.

The sentinel studies utilizing TCD to identify and grade the severity of SCA-associated vasculopathy in the USA reported, in 315 children, conditional risk studies in 30 children (9%) and high risk in 25 children

TABLE 3 Stroke incidence by transcranial Doppler ultrasound risk classification in the USA versus reported results in African children.

	TAMMX subnormal (MCA/ICA <50 cm/s)	TAMMX normal (MCA/ICA <170 cm/s)	TAMMX conditional (MCA/ICA 170–199 cm/s)	TAMMX abnormal (MCA/ICA ≥200 cm/s)	Overall
USA					
Adams et al. (*n* = 315)	N/A	260 (83%)	30 (9%)	25 (8%)	
Stroke incidence at 40 months	N/A	5 (2%)	2 (7%)	10 (40%)	17 (5.3%)
Kenya					
Makani et al. (2009) (*n* = 105)	7 (7%)	95 (90%)	3 (3%)	0 (0%)	
Stroke incidence at 36 months	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DRC, Zambia, Malawi					
O'Brien et al. (current) (*n* = 770)	34 (4%)	604 (78%)	129 (17%)	3 (0.4%)	
Stroke incidence at 15 months	4 (12%)	6 (1%)	7 (5.4%)	0 (0%)	17 (2.2%)

Note: The other studies in Table 2 do not include stroke incidence rates.
Abbreviations: DRC, Democratic Republic of the Congo; ICA, internal carotid artery; MCA, middle cerebral artery; *n*, number; N/A, not applicable; TAMMX, time-averaged maximum of the mean.

(8%) [3]. Our study identified, in a stroke-free cohort, a significantly higher frequency of conditional risk studies and a lower frequency of high-risk studies than was reported in the USA. Our findings are largely supported by other studies of African children with SCA who have undergone TCD examination (Table 2). Similar high rates of conditional studies are reported across most countries. However, there may be regional variation in rates of high-risk examination results (Table 2). Most studies from Nigeria report similar rates of high-risk studies to what was reported in the original work by Adams et al. [17–20]. In contrast, work from Kenya, Tanzania, and Uganda shows similar low rates of high-risk studies to what we identified in our cohort [21–24].

In the original work in the USA, 17/315 (5.3%) children developed stroke over a mean study follow-up period of 64 months, with the stroke incidence varying depending on TCD risk classification (40% in those with a high-risk study, 7% in those with a conditional risk study, and 2% in those with a low-risk study). Our study highlights the extreme paucity of data on prospective stroke incidence in African children with SCA by TCD risk stratification category (Table 3). Makani et al. followed 95 children for 3 years, 11 (11.5%) of whom died of unknown causes, but reportedly none suffered stroke [21]. Our cohort was only followed for 15 months, but in that period, overall stroke incidence was 2.2% (5.4% in those with a conditional risk study and 12% in those with unknown risk categorization). However, this short duration of follow-up is insufficient to determine true stroke incidence.

A meta-analysis reported stroke prevalence rates in African children being seen for routine follow-up at SCA clinics. No TCDs were done. By country, stroke prevalence was as follows: Nigeria 2.9%–9.1%, Cameroon 6.7%, Uganda 6.2%, Malawi 8.5%, and Tanzania 16.9% [1]. The authors noted that given the poor survival of stroke in resource-limited settings, these values likely grossly underestimated the true incidence of stroke in children with SCA in Africa. If very few of these children would have had an abnormal TCD examination (as results shown in Table 2 suggest may be the case, at least regionally in central/east/southern Africa), the near entirety of the stroke rate reported may have been in those with conditional, low, or unknown risk studies. Clearly, this is an extrapolation, but the possibility underscores the importance of future work that longitudinally follows African children with SCA and determines stroke incidence by TCD categorization. This work should also explore genetic or clinical risk modifiers by TCD category to fully inform the development of future screening and treatment guidelines.

TABLE 4 Possible stroke determinants in African children with sickle cell anemia.

Possible determinant	Potential intervention
Vasculopathy	Chronic transfusion Hydroxyurea
Anemia	*Improve baseline hemoglobin* Improved routine screening of hemoglobin at outpatient visits Nutritional support Regular deworming *Prevent rapid drops in hemoglobin* Malaria chemoprophylaxis
Fever/infection with increased cerebral metabolic demand and inflammation	Early antibiotics for bacterial infection Improved access to and utilization of anti-inflammatories
Acute chest syndrome with hypoxia and inflammation	Improved access to oxygen Improved access to and utilization of anti-inflammatories
Pain crises with increased metabolic demand and inflammation	Improved access to and utilization of anti-inflammatories Improved access to and utilization of opioids
Genetic modifiers of disease—G-6-PD	Improved screening for G-6-PD deficiency and if positive, avoidance of medication triggers

Abbreviation: G-6-PD, glucose-6-phosphate deficiency.

Reasons for the differences in TCD findings in our cohort of African children with SCA compared to African American children are unknown. Given a paucity of newborn screening programs and

limited access to continuous standard of care, it is possible that the most severely affected children with SCA (with high hemoglobin SS concentrations), who would also develop severe vasculopathy and an abnormal TCD, died without a diagnosis of SCA or died due to other complications of the disease early in childhood before vasculopathy developed [25]. This would then increase the overall rate of conditional/low-risk studies. This may be supported by the finding that previous studies in Nigeria report more similar rates of abnormal studies to what was seen in the USA, whereas other locations in Africa report similar findings to what we identified. Nigeria, with a higher gross domestic product than many other nations and a very high prevalence of SCA, may have improved access to high-quality, comprehensive care for SCA, decreasing mortality from other complications.

Regarding stroke in African children with conditional or low-risk studies, it is important to understand all potential pathophysiologic contributors to stroke (Table 4). Cerebral infarction results from an imbalance between energy supply (cerebral blood flow and oxygen delivery) and demand (cerebral metabolic rate of oxygen consumption) [26, 27]. Thus, other factors beyond the degree of vasculopathy limiting cerebral flow may contribute to the development of stroke. Dowling et al. enrolled children with SCA admitted with acute, severe anemia with hemoglobin levels <5.5 g/dL and performed follow-up diffusion-weighted magnetic resonance imaging within 10 days [28]. In the cohort, 18.2% (four of 22) had new ischemic lesions of the brain. Stroke secondary to impaired oxygen delivery in the setting of severe acute anemia was demonstrated. Baseline hemoglobin concentrations are often lower in children with SCA in SSA than in other settings [29]. This likely occurs secondary to nutritional deficiencies, chronic intestinal parasitic infections, and inadequate access to monitoring of and treatment for SCA [30–32]. Acute, significant drops in hemoglobin are also more commonly encountered in SSA than in other settings due to recurrent malarial or other infections [32]. Inadequate oxygen delivery in the setting of low baseline hemoglobin exacerbated by frequent, acute episodes of anemia may contribute to stroke in African children with SCA at a more modest degree of vasculopathy (i.e., represented by low or conditional risk studies). SCA-related stroke is also commonly followed within days of the onset of fever, infection, acute chest syndrome, and pain crises in any setting [1]. In SSA, decreased availability and utilization of anti-inflammatories, opioids, and oxygen therapy in the management of acute disease-related complications is nearly uniform [33]. Thus, untreated inflammation, elevated cerebral metabolic demand in the setting of uncontrolled fever or poor pain control, and untreated hypoxia due to limited access to supplemental oxygen during episodes of pain crisis or acute chest syndrome may contribute to a higher stroke risk in African children with SCA than is seen in other populations, even in the absence of severe vasculopathy. Various genetic modulators are also known to affect the phenotype of SCA, with patients manifesting differing degrees of clinical severity [34, 35]. In other populations of patients with SCA, the severity of vasculopathy and stroke occurrence may be worse in the setting of glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency [34–38]. G6PD deficiency is reported in 10%–20% of Africans and may increase primary stroke occurrence in African children with SCA regardless of underlying TCD flow velocities [32, 35, 38–41].

This study identified a significant number of children with subnormal CBFVs (TAMMX <50 cm/s). CBFVs measured by TCD become elevated and then profoundly reduced below the normative value as the degree of arterial narrowing progresses beyond ~80% (Figure 1). Thus, the low CBFVs reported may represent those with severe vasculopathy. It is also possible that technical limitations resulted in a low measured TAMMX in the absence of vasculopathy, although all training to avoid this was provided to practitioners performing examinations. A prospective cohort study is needed to determine if low CBFVs (<50 cm/s) represent a category that represents profound

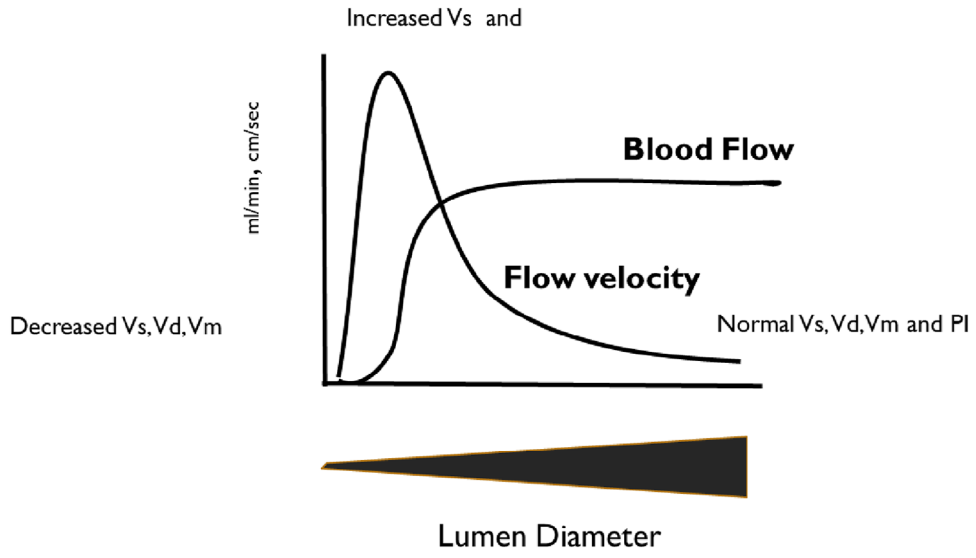

FIGURE 1 Spencer's curve explaining the relationship between vessel lumen diameter reduction, cerebral blood flow, and measured cerebral blood flow velocities on transcranial Doppler ultrasound.

vasculopathy and thus may be associated with high stroke risk in African children.

One significant limitation of this study was that we did not prospectively, longitudinally follow for stroke development over 3–5 years, the timeframe likely necessary to capture data that allows for determination of true stroke incidence. This was not possible as the funding mechanism only provided two years of funding for this exploratory work. Future studies with long-term follow-up are necessary to determine stroke risk in low, conditional, and unknown/subnormal TCD risk categorizations and potential clinical or genetic modifiers of that risk. Additionally, only MCA and terminal ICA were evaluated. Anterior cerebral artery, posterior cerebral artery, or carotid artery stenosis may also be associated with increased stroke risk, albeit not commonly. By not including a full TCD examination, we may have missed stenosis in these vessels that contributed to neurologic symptom development in those otherwise classified as low or conditional risk. Future studies should include full examinations.

Another limitation was in the children that we did identify as having previous stroke or new neurologic symptoms, which was determined by WHO criteria gathered on questioning of caregivers. We did not assess a Pediatric NIH Stroke Scale and thus may have misclassified some individuals. Future prospective studies with the primary endpoint of stroke development should include this assessment. Last, TCD is operator dependent with the results dependent on technicians' skill. We carefully ensured that a degree of expertise was obtained before practitioners began collecting data for this work, and all studies were centrally reviewed and scored for quality. However, some variability of results may have occurred given the number of operators performing exams.

5 | CONCLUSIONS

African children with SCA were identified to have a low rate of high-risk TCD screening results, but a high frequency of conditional risk studies. Over a short follow-up period, stroke incidence was modest, but all strokes occurred in children with conditional, low, or unknown TCD risk categorization. Establishing clear TCD cut-offs values and/or alternate risk factors that determine stroke risk in African children with SCA is necessary to allow for the development of evidence-based screening guidelines for use on the continent. Future trials can then focus limited resources on the children most likely to benefit from intervention and reduce overall morbidity and mortality from SCA-related stroke in SSA.

AUTHOR CONTRIBUTIONS

Each author contributed to the manuscript in significant ways, such as patient identification, enrollment, performance of TCDs, data entry, and manuscript preparation. All authors have reviewed and agreed upon the manuscript content.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health Fogarty International Center (1R21HD106252-01).

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (N.O.). The data are not publicly available due to their containing information that would compromise the privacy of the research participants.

ETHICS STATEMENT

Ethics approval was obtained in each country (DRC CES ID 279/CNES/BN/PMMF/2021, Zambia ERES ID 00005948, Malawi COMREC waived need for consent and incited standard of care).

PATIENT CONSENT STATEMENT

Study participants were minors, so consent was obtained from guardians prior to participation. Study assent was obtained for participants over the age of 8 years.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No material was taken from other sources.

CLINICAL TRIAL REGISTRATION

The trial was not registered.

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How to cite this article: O'Brien NF, Moons P, Johnson H, Tshimanga T, Musungufu DA, Ekandji RT, et al. Transcranial Doppler ultrasound velocities in a population of unstudied African children with sickle cell anemia. eJHaem. 2024;5:3–10. https://doi.org/10.1002/jha2.818