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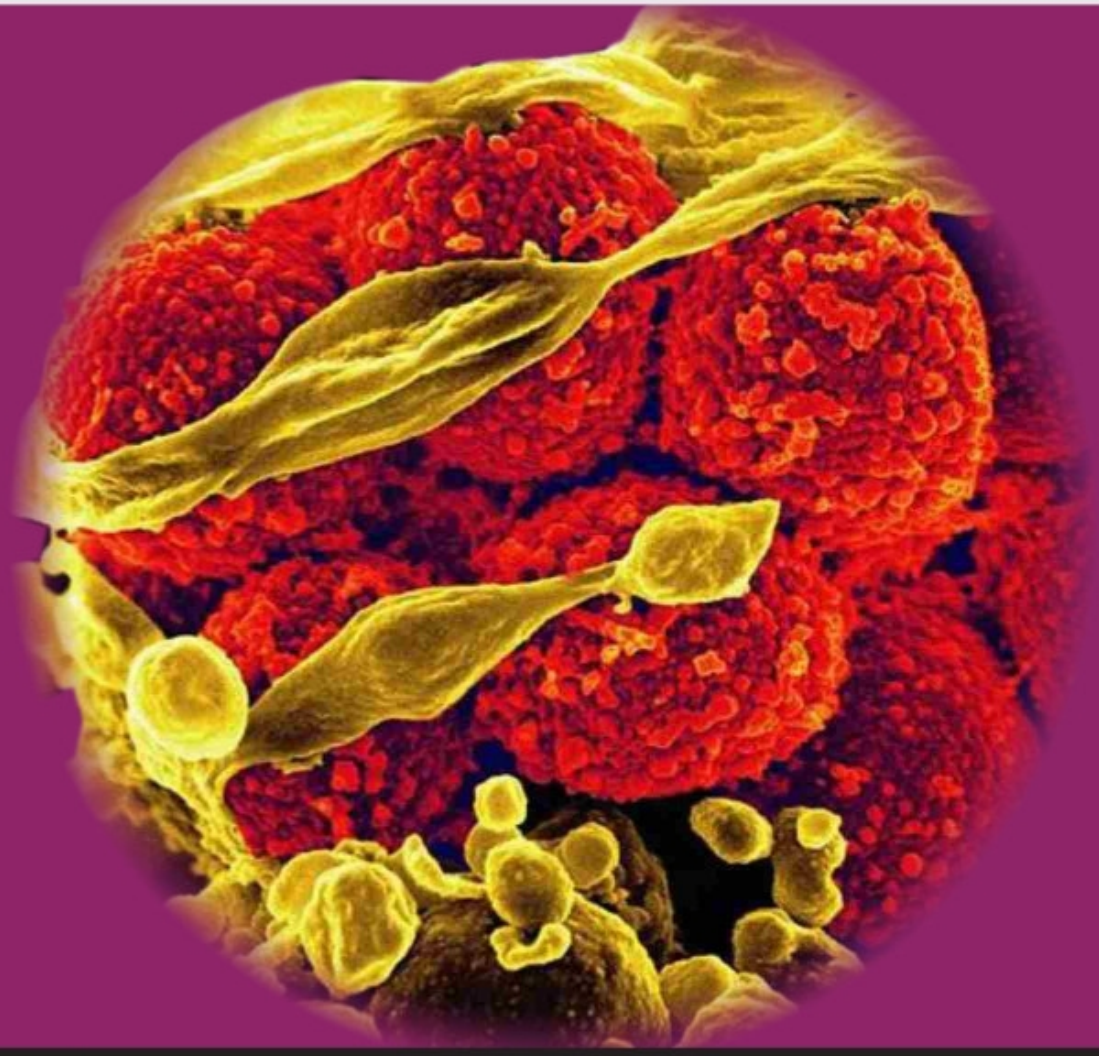

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REVIEW ARTICLE

Role of Transcranial Doppler in Assessment of Intracranial Blood Velocities in Children with Sickle Cell Disease: A Review of the Nigerian Experience

[1]Itanyi UD, [2]Galadanci NA, [3]Nnodu OE

[1]Department of Radiology, University of Abuja Teaching Hospital, Gwagwalada, Abuja;
[2]Department of Haematology and Blood Transfusion, Aminu Kano Teaching Hospital, Kano;
[3]Department of Haematology, University of Abuja Teaching Hospital,
Gwagwalada, Nigeria.

Corresponding Author:
Itanyi Ukamaka D.,
Department of Radiology,
University of Abuja Teaching hospital
Gwagwalada, Abuja
amakaitanyi1995@gmail.com

SUMMARY

Stroke is a devastating and yet preventable sequelae of intracranial vasculopathy in children and adults with sickle cell disease. Transcranial Doppler (TCD) ultrasonography is an established imaging modality for monitoring of intracranial vascular velocities and stratification of children with sickle cell disease based on the velocities into different risk groups with the aim of identifying those at high risk of stroke. Blood transfusion therapy and Hydroxyurea have been successful in the primary prevention of stroke. Transcranial Doppler screening is the standard of care in the United States and other developed countries, but poorly utilized in Nigeria with only a few centres having availability of TCD ultrasound. This traditional review article highlights the basic intracranial vascular anatomy, TCD protocol and current practices of intracranial vascular velocity screening and stroke prevention in Nigeria.

Keywords: Transcranial Doppler (TCD), stroke, sickle cell disease, Nigeria.

INTRODUCTION

Sickle cell disease (SCD) is a chronic genetic disorder that occurs with the substitution of valine for glutamic acid in the sixth amino acid position of the β-globin chain, homozygous inheritance leads to abnormal Hb S known as Sickle Cell Anaemia (SCA), the most severe form of the disease.[1] The resulting abnormality in the form of poor oxygen carrying capacity of haemoglobin leads to chronic anaemia and vaso-occlusive events with subsequent tissue ischaemia.

Stroke is a sudden occurrence of neurologic symptoms as a result of brain ischaemia secondary to occlusion or rupture of an intracranial artery. It is a major cause of morbidity and mortality in children with SCD. The vaso-occlusive process in SCD is complex and is mediated by red cell and leukocyte adhesion, inflammation, oxidative stress, and a hypercoagulable state, all resulting in endothelial injury and dysfunction.[2] Vasculopathy in the brain is often associated with larger vessels primarily localized to the distal supraclinoid internal carotid artery and the proximal portions of the middle and anterior cerebral arteries with such lesions being demonstrated in about 80% of angiograms of patients with sickle cell anaemia and stroke.[3]

The affectation of the large vessels will lead to overt stroke, which could be infarctive or haemorrhagic while affectation of the smaller penetrating arteries leads to micro infarcts without any overt neurologic symptom (silent stroke). Clinical ischaemic strokes in patients with SCD are associated with prior transient ischaemic attack, increased systolic blood pressure, acute coronary syndrome, prior silent infarcts, and nocturnal hypoxaemia. However, haemorrhagic stroke, which occurs in a third of SCD related stroke patients is associated with older age, low steady state haemoglobin, low steady state leucocytes count, transfusion within 2 weeks, and treatment with corticosteroids or non-steroidal anti-inflammatory drugs within 2 weeks.[4] Silent

infarcts are associated with leukocytosis, seizures, lower baseline haemoglobin, male sex, and hypertension.[4] Progressive stenosis of the Internal Carotid Artery (ICA) and its branches with compensatory basal collaterals is seen in Moya Moya syndrome and occurs in 20-30% of patients with SCD.[5] It is radiologically seen as a 'puff of smoke' on angiograms and predisposes to both ischaemic and haemorrhagic stroke.

Epidemiology

Stroke is one of the most important and devastating complications of SCD with varying prevalence in different study locations. (Table 1). Stroke is 221 to 300 times more frequent in patients with SCD when compared to healthy children, especially in children with SCA under the age of 20, with the greatest incidence between 4 and 15 years of age.[6] The Cooperative Study of Sickle Cell Disease study showed that the highest rates of prevalence of cerebrovascular accidents (CVA; 4.01%) and incidence (0.61 per 100 patient-years) occurred in sickle cell anaemia (SCA) patients.[7] Infarctive CVA was lowest in SS patients 20 to 29 years of age and higher in children and older patients, while the incidence of haemorrhagic stroke in SS patients was highest among patients aged 20 to 29 years with mortality rate of 26% in the 2 weeks after haemorrhagic stroke occurring across all age groups. The chances of having a first CVA by 20 years of age, 30 years of age, and 45 years of age were estimated at 11%, 15%, and 24%, respectively, for SS patients.[7]

The Jamaica cohort study recorded 10 recurrent episodes at a median interval of 9 months after the initial event noting that a high leukocyte count and an acute decrease of haemoglobin were risk factors for stroke in patients with homozygous disease.[8] More than 75% of the global burden of SCA occurs in sub-Saharan Africa. [9] The first systematic review and meta-analysis to summarize prevalence data on the neurologic complications of SCD in Africa showed overall stroke prevalence rates of 4.2% in a pooled sample of 18,977 participants from 23 studies.[10]

A study conducted in Yaoundé, Cameroon showed cerebral infarction to be three times as common as cerebral haemorrhage. Cerebral infarction was more frequent in patients aged below 20 years and haemorrhage in those above 20 with annual recurrence rate of 25% without any form of prophylaxis.[11] The prevalence of stroke in hospitalized Ugandan children with SCA was 6.8 %. Children with stroke were often admitted with other medical conditions such as severe anaemia, bacteraemia and vaso-occlusion.[12]

Sickle cell disease is the most common inherited genetic disorder affecting Nigerians with an estimated 20–25% of the prevalence of the population having the sickle cell trait and about 2–3% of children born annually with the disease.[13] Prevalence of stroke among Nigerian children with SCD is estimated to be between 5 - 7% and it is estimated that 40–75% of children with SCD who suffer a first stroke will have a recurrence without any intervention.[13-16] Fatunde *et al* [13] in Ibadan Nigeria showed that SCD was responsible for 87% of stroke seen in children with a high recurrence rate of 61.5% after an average of 25.6 months in the studied cohort. A later multicenter study done by Jude *et al* [17] showed the overall prevalence of stroke to be 12.4 per 1000; with a lower recurrence rate of 23.9%. This stroke prevalence data was obtained from 14 physicians working in 11 tertiary health centres across Nigeria. Prevalence in the adult patients was 17.7 per 1000 patients and 7.4 per 1000 patients in children. The average age incidence of stroke was 21 years in adults and 6 years in the children. The stroke prevalence varied from zero in the adults seen at Nnewi, Anambra State, and Port Harcourt, Rivers State, to as high as 150 per 1000 patients in Ogbomosho, Oyo State.[17] The prevalence amongst paediatric patients obtained in this study is similar to that obtained by Izuora *et al* [18] in Enugu, where a rate of 6.5 per 1000 was determined. This is lower than the value obtained by Adegoke *et al* [19] in Ilesha, Osun State, South-West Nigeria, Jiya in Sokoto,

Sokoto State [20] and George *et al* [21] in Port Harcourt, who reported rates of 2.9%, 3.6% and 4.3% respectively. The mean age of stroke occurrence was between 6.3 and 6.8 years from these studies, [15,16,20] with a mean time of hospital presentation after the stroke onset of 10 (±2.5) days.[20]

TABLE 1: Characteristics of studies with stroke prevalence rates in SCD

PUBLICATION	LOCATION OF STUDY	YEAR OF STUDY	AGE RANGE (YEARS)	SAMPLE SIZE	STROKE PREVELANCE (%)
GASTON[7]	United States of America	1978-1988	<25	4,082	4.01
BALKARAN[8]	Jamaica	1992	9-17	310	7.8
NJAMNSHI[11]	Yaounde, Cameroon	Oct-Dec 2003	7/12-35	120	6.67
MUNUBE[12]	Uganda	2012-2014	<18	2176	6.8
FATUNDE[13]	Ibadan, Nigeria	1988-2002	2-16	500	5.4
KEHINDE[14]	Lagos, Nigeria	July 2004 - June 2005	4-19	322	5.2
LAGUNJI[15]	Ibadan, Nigeria	July 2009 - June 2011	1-16	214	8.4
ONIYANGI[16]	Abuja, Nigeria	Jan 2009 - June 2012	2-14	596	5.2
JUDE [17]	Multicentre, Nigeria	2014	<18	2955	7.4
ADEGOKE[19]	Ilesha, Nigeria	Jan-Dec 2013	0.5-15	240	2.9
JIYA[20]	Sokoto, Nigeria	May 2004 - April 2014	0-15	416	3.6
GEORGE[21]	Port Harcourt, Nigeria	Jan 2005 - Dec 2009	6/12-16	256	4.3

Anatomy of the Circle of Willis

The intracranial structures are supplied by the internal carotid artery (ICA) and its branches which form the anterior circulation and the vertebrobasilar arteries and branches which make up the posterior circulation. Communication between these two circulatory pathways is provided by the circle of Willis which forms a natural collateral conduit, through which blood is diverted in case of proximal vessel occlusion. The intracranial portion of the ICA divides into the anterior cerebral arteries (ACA) and the middle cerebral arteries (MCA). The ACA on both sides communicates with each other through the anterior communicating (ACOM) artery. The right and left vertebral arteries unite to form the basilar artery, which in turn divides into the right and left posterior cerebral arteries (PCA). The ICA on either side is connected with the PCAs by posterior communicating arteries, to complete the posterior part of the circle of Willis. These vessels may be visualized by angiography as well as some non-invasive and less expensive modalities such as Doppler sonography.

Imaging versus Non-imaging Transcranial Doppler

Transcranial Doppler is based on the ability of the probe to emit high frequency sound waves, which are in turn reflected by the moving blood cells within the vessels. The difference between the waves is called “Doppler shift” frequency and is directly proportional to the blood flow velocity. This is displayed on the TCD monitor as a spectrum of the different velocities of the red blood cell which can be electronically calculated. The specific parameters obtained from this spectral analysis include peak systolic velocity (Vs), end diastolic velocity (Vd),

systolic upstroke or acceleration time, pulsatility index (PI), and time-averaged mean maximum velocity (V_{mean}).[22]

Flow velocity is directly related to cerebral blood flow (CBF) and inversely related to arterial diameter therefore increased intracranial velocity is usually an evidence of stenosis. The gradual progression of stenosis in sickle cell vasculopathy leaves a window for detection of velocity abnormalities before onset of stroke symptoms. Abnormal Increase in intracranial vascular velocity is a predictive factor for stroke in sickle cell patients and can be detected by Doppler Ultrasonograhic imaging. This non-invasive and non-ionizing modality is a major breakthrough in the investigation of sickle cell related vasculopathy and allows identification of high risk asymptomatic children with the disease.

There are currently two types of TCD machines used for intracranial velocimetry; these are the non-imaging/non-duplex (TCD) and imaging/duplex systems (TCDI). In non-duplex devices, vessel identification based on waveform pattern, audible Doppler shift depth, and insonation angle of Doppler sample volume.[23] There is no anatomical visualization of the intracranial structures (Figure 1). The duplex/imaging system on the other hand allows visual outline of the parenchyma, identification of the vessels and flow direction in relation to the probe. (Figure 2) A comparison of the two imaging systems are made in Table 2.

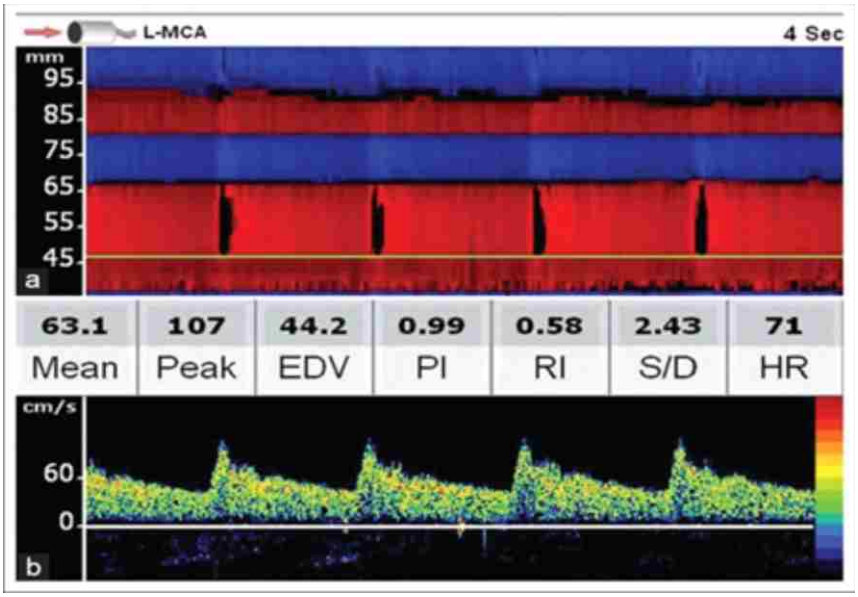

Figure 1: Non-imaging screen showing the M-mode appearance of various arteries.

Key: end diastolic volume (EDV), pulsatility index (PI), resistivity index (RI), systolic/diastolic ratio (S/D), heart rate (HR). (a) MCA is red signal up to 65 mm, ACA is blue signal from 65 mm to 80 mm; Contralateral A1 ACA is red signal beyond 80 mm; Contralateral MCA is blue signal beyond 92 mm. (b) normal TCD spectrum at a depth of 47 mm. Note the rapid systolic acceleration and stepwise deceleration during the diastole and significant end-diastolic velocity.[15]

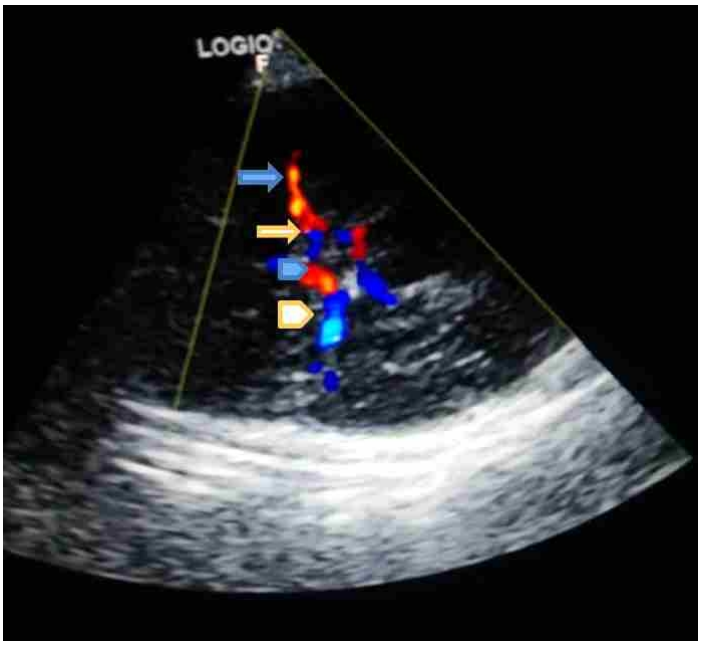

Figure 2: TCDI showing Circle of Willis. Blue arrow: MCA; orange arrow: CA; Blue arrowhead: Contralateral ACA; orange arrowhead: contralateral MCA

Table 2: Comparison of Imaging (TCDI) and Non Imaging Doppler Systems (TCD)

TCDI	TCD
Allows visual identification of the vessels and flow direction in relation to the probe.	Gives information regarding tissue motion and blood flow velocities without visualization of the intracranial structures.
Higher cost of machine since it incorporates different probes for imaging of other parts of the body	Relatively lower cost of machine since it is specific for intracranial vascular examinations
Allows for recording of lower velocities	Allows recording of mean velocities in excess of 300cm/s
The larger footprint is disadvantageous in smaller temporal windows.	The transducer foot print is small and therefore useful for small temporal windows
It enables an operator to determine an angle between the course of an artery and the ultrasound beam and correct measurements for cosine of the angle	Vessels are not directly visualised and identification depends on waveform pattern seen on the monitor, sound of the doppler shift, depth of the wave and insonation angle of Doppler sample volume
Since most sonologists are already used to the machine, a lesser curve of learning is expected.	Longer learning curve since greater expertise is needed to identify the vessels and record the readings
Angle of insonation is usually placed at < 30 degrees to minimize error in electronic readings.	Manual measurements and recording protocols are used
Readily available in ultrasound machines with colour flow capabilities	Not available in most centres

TCDI has the potential to be more accurate in the estimation of risk of stroke because, in contrast to TCD, it allows outlining of parenchymal structures and visualization of the examined vessels. [23] Studies have noted significant differences in the intracranial velocities when comparing TCDI and TCD. A study done to compare angle-corrected, uncorrected TCDI, and TCD blood flow velocities in 37 children with SCD confirmed that the TCDI velocities were lower by about 20% compared with the TCD velocities though, the angle-corrected TCDI velocities do not differ significantly from the respective TCD velocities.[24] They also noted that the risk of inaccurate velocity sampling with TCD is higher

than with TCDI. Bulas *et al* [23] noted that TCDI values were most similar to the TCD values in the MCA (-9.0%) and ICA (-10.8%), with greater variability in the ACA (-19.3%), bifurcation (-16.3%), and BA (-23.1%). Risk grouping of the patients did not change with the two methods. Based on similarity of studies using TCDI, McCarville *et al* [25] suggested that 180 cm/sec or more should be considered abnormal and 153–179 cm/sec, as conditional. These values are 10% lower than those obtained from the nonduplex equipment used in the STOP study. These figures should be taken into consideration when using imaging TCD.

Intracranial Velocimetry

In view of the relatively high prevalence rate of stroke in children with SCA, several effective screening programmes have been adopted for early detection of at risk patients with the aim of primary prevention of strokes. Currently, primary stroke prevention in children with SCA involves the use of TCD to determine those at risk of their first stroke by measuring the CBF velocity in the MCA and/or ICA.

The STOP study, a randomized controlled clinical trial, done on children with SCA aged between 2 and 16years with abnormal results on TCD, confirmed the reliability of non - imaging TCD in identification of children with the highest risk of stroke and established that chronic transfusion therapy can reduce the risk of a first stroke by 92% in these high-risk children [26].The trial protocol used a non-imaging 2-MHz pulsed Doppler for assessment and stratification of patients using transtemporal and sub-occipital approaches.

In the STOP trial, using the highest measurable Vmean, stroke risk was classified as follows:

1) Normal risk (NR): all recordings lower than 170 cm/s
2) Conditional risk (CR): at least 170 but lower than 200 cm/s)
3) Abnormal: Vmean of at least 200 cm/s in either the ICA or MCA.
4) Inadequate if readings were not provided on either sides.

Very low values (<70 cm/s) may be as a result of severe stenosis.

Adams *et al* [27] demonstrated that children with Vmean of >200 cm/s in the distal ICA or proximal MCA had a stroke risk that was 10—20 times that of the general sickle cell population of the same age. The study therefore recommended that those with abnormal velocities should undergo repeated screening within the next few weeks and if the second measurement is also abnormal should be offered chronic transfusion therapy; those with conditional velocity should be rescreened within 3-6 months, while those with normal studies could be rescreened yearly.

The Nigerian Experience

Compared with African-American children, Nigerian children with Hb SS disease have been found to have considerably higher prevalence of CR velocities [28] hence higher risks of developing a stroke. A few studies have reported the values of cerebral blood flow (CBF) in patients with SCD in Nigeria with prevalence of abnormal velocities ranging from 3-10.8 % (Table 3) .[16, 28-32] Adekunle *et al* [31] in Lagos showed that prevalence of abnormal Vmean was seen solely in Hb SS patients. The Vmean were 163±25 cm/sec, 162±30 cm/sec and 150±30 cm/sec for children<5 years, 5-10 years and 11-16 years respectively. [31] Clinical predictors of abnormal CBF velocity include elevated blood pressure and transcutaneous arterial oxygen saturation less than 95%, low haematocrit, low haemoglobin concentration, leucocytosis, reticulocytosis and high lactate dehydrogenase. [28,31,32]

Table 3: Cerebral flow velocities in Nigerian children with SCD

PUBLICATION	TYPE OF MACHINE	STUDY LOCATION	YEAR OF STUDY	AGE RANGE (YEARS)	SAMPLE SIZE	ABNORMAL (%)	CR (%)	NR (%)
ONIYANGI[16]	TCDI	Abuja, Nigeria	Jan 2009-June 2012	0-16	129	6.9	11.6	81.4
LAGUNJU[28]	TCD	Ibadan, Nigeria	2011	3-16	145	4.7	19.7	75.6
SOYEBI[29]	TCD	Lagos, Nigeria	March 2011-Sept 2013	2-16	3331	9.3	19	70.4
USORO[30]	TCD	Lagos, Nigeria	Oct 2014-March 2015	0-16	200	3.5	36	60.5
ADEKUNLE[31]	TCD	Lagos, Nigeria	July-Nov 2015	2-16	368/388	10.8		81.4
ISMAIL[32]	TCD	Northern Nigeria	2019	2-16	100	3	11	84

Following the World Health Organization's recommendation that 50% of member states should establish SCD control programs by 2020, [33] the Federal Government of Nigeria formulated and launched the National Guidelines for the Control and Management of Sickle Cell Disease) on November 28, 2014 followed by the development of a program of implementation of evidence based interventions for the prevention and control of SCD in our setting.[34]

Recommendations for the primary prevention of stroke include:

a) All SCD children aged 2-16 years should have TCD. b) Repeat TCD in 3 months in cases with a velocity of 170-199cm/s. c) In those identified with the high risk, stroke should be prevented with hydroxyurea or hypertransfusion (i.e. transfusion given every 3-4 weeks).

Despite the success rate established with use of chronic blood transfusion (CBT) as the gold standard for primary stroke prevention, Adams *et al* [27] noted that the long-term benefit of this approach may be limited by the cost and complications of transfusion. Although, it is unclear for how long transfusion should be continued as a means of preventing stroke in children with SCA.[27] Chronic blood transfusion (CBT) for stroke prevention in Nigerian children has been fraught with challenges. High economic costs, unavailability of blood, need to regularly seek for blood donors, cultural beliefs and fears and high frequency of transfusion reactions are major challenges to a successful CBT program in Nigeria. In a study by Lagunju *et al* [35] at Ibadan, Oyo State, and Oniyangi *et al* [16] in Abuja, none of the children with abnormal TCD velocities consented to CBT. Similar limitations were noted in Sokoto, where more than a quarter of the patients in the study did not receive CBT and more than half of those who started CBT could not sustain it.[36] Studies have shown the efficacy and simplicity of hydroxyurea, a myelosuppressive chemotherapeutic agent, as an alternative to blood transfusion in high-risk patients on the basis of TCD with significant reduction in increased flow.[37] A multicentre, phase 3, randomized, open-label, non-inferiority trial was conducted at 26 paediatric hospitals and health centres in the USA and Canada (TWiTCH trial) to compare hydroxyurea with standard transfusion in children with SCA and abnormal TCD flow velocities (≥ 200 cm/s), but no severe vasculopathy. They concluded that for high-risk children with SCA and abnormal TCD velocities who have received at least 1 year of transfusions and have no Magnetic Resonance Angiography (MRA)-defined severe vasculopathy, hydroxyurea treatment could substitute for chronic transfusions to maintain TCD velocities and help to prevent primary stroke.[38]

In the United States of America, the National Institutes of Health (NIH) funded Sickle Cell

Disease Stroke Prevention in Nigeria (SPIN) trial, children with SCA and TCD velocity≥ 200 cm/sec in the middle cerebral arteries underwent a single arm internal pilot of hydroxyurea to determine its acceptability and safety for primary stroke prevention. Twenty-five children received moderate-dose hydroxyurea therapy, 20 mg/kg per day for 3 years. The results of the study showed that reduction in cerebral blood flow velocity and stroke risk occurred within 3 months of initiating therapy in ~ 85% of the participants. The median TCD velocity among those who had hydroxyurea therapy declined from 211 at baseline (n = 27) to 165 at 24 months (n = 25). [39] The success of hydroxyurea therapy for stroke prevention in SCD has been recorded in other studies in Nigeria.[40, 41]

With a population of greater than 160 million, highest number of children with SCD in the world, and a relatively high prevalence of primary strokes and recurrence, it is expected that this simple and cost- effective screening recommendations and early treatment programmes should be established. Despite the globally established recommendations of routine screening for stroke risk by non-imaging Doppler, this recommendation is not being implemented in Nigeria due to non-availability of the machine and poor access to the few centres where the machines are available. This lack of sustainable efforts towards tackling the prevention of this devastating complication, should be urgently addressed by the provision of TCD sonographic equipment It has been shown that effective capacity building of middle level manpower is feasible and could provide a credible TCD screening service to communities with a high demand and a shortage of trained professionals.[29]

CONCLUSION

Stroke is a devastating and yet preventable sequelae of intracranial vasculopathy in children and adults with SCD. Despite the ability to detect children with SCD at increased risk of stroke with TCD and the demonstration that hydroxyurea may be used to reduce this risk where blood services are suboptimal, only a few health institutions in Nigeria have the facilities and trained personnel to offer this service. This gap in the management of children with SCA in health institutions in Nigeria needs to be urgently addressed in order to prevent disability. Comparative studies of imaging and non-imaging TCD should be conducted with a view to harmonizing the readings and obtaining values that could be used in this environment.

Conflict of Interest:
The authors have no conflict of interest.

Author's Contributions:
This review was conducted by IUD, GNA, and NOE. NOE was involved in the concept, study design and final review; IUD was involved in writing and research while GNA was involved in additional corrections.

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