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## Strokes in children with sickle cell disease at the National Hospital Abuja Nigeria

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**Abstract Background:** Strokes occur in sickle cell disease (SCD), and are associated with significant morbidity and mortality.

**Objectives:** To determine the prevalence of strokes amongst children with SCD, and document the major clinical features, complications, effect of treatment with chronic transfusion therapy (CTT) and outcome.

**Methods:** A descriptive retrospective study of SCD children with strokes seen at the National Hospital Abuja, Nigeria over a 2.5 year period from January 2009 – June 2012. Data was collected by scrutinizing case files obtained from the hospital medical records unit. Information obtained included demographic data, clinical features, packed cell volume (PCV), brain imaging, long term neurologic deficits, effect of CTT, stroke recurrence and outcome.

**Results:** There were 31 children with strokes among 596 children with SCD documented in the register, giving a prevalence of 5.2%. Twenty six (26) case notes were retrieved. There were 12 males and 14 females, M: F ratio of 0.9:1; mean age was 6.4 years (SD 3.4) range: 1 year 7 months – 14 years; mean PCV at the time of strokes was 21.1% (SD 3.9) range 14 – 29%. All (100%) had Haemoglobin SS on electrophoresis. Presentations were convulsions 18, inability to use limbs 11, weakness of limbs 10; long term neurological deficits were hemiplegia 11, cognition loss 11. Three (3) children had no deficits. Brain imaging (Computed Tomography Scan and Magnetic Resonance

Imaging) done in 16 (61.5%) children showed cerebral atrophy in 10, acute cerebral infarcts in 9, chronic cerebral infarcts in 6, acute intra cranial haemorrhage in 1 and normal imagings in 4 children.

Twelve (12) children (46.2%) children had recurrences of stroke ranging in number from 1 to 4, which occurred 6 months to 3 years after the initial stroke. There were no statistical significant differences between the children with recurrences of stroke compared to those without regarding the age, sex, weight or PCVs  $p > 0.05$ .

Fifteen (15) children (57.7%) were enrolled in CTT. Two (2) out of 7 children (28.6%) that had regular CTT had stroke recurrence; compared to 5 out of 11 children (45.4%) with no CTT ( $p > 0.05$ ). Four (4) out of 6 (66.7%) children with irregular CTT and 1 of 2 children who stopped CTT had stroke recurrence.

**Outcome:** 17 children were alive, 7 were lost to follow up, 1 died and 1 was referred to another center.

**Conclusion:** Strokes were an important cause of morbidity in Nigerian children with SCD, with major long term neurologic deficits. CTT appeared beneficial in preventing stroke recurrences. Primary prevention strategy by Trans Cranial Doppler ultrasound studies of the cerebral arteries, with the aim of promptly initiating appropriate preventive therapy for stroke is strongly advocated.

**Key words:** Sickle cell disease, Stroke, Children, Chronic Transfusion Therapy

## Introduction

Strokes (cerebrovascular accidents CVA) are potentially devastating consequences of sickle cell disease (SCD), which have been associated with significant morbidity and mortality.<sup>1</sup>

The reported risk of a first stroke in SCD is up to 0.85 per 100 patient years in the first 20 years of life,<sup>1-5</sup> with a prevalence of up to 11.5%.<sup>1-9</sup> Recurrence rates of 14%<sup>6</sup> - 61.5%<sup>1,3,5-7,9</sup> have been reported from developed and developing countries including Nigeria respectively. They commonly occur in children up to 14 years of age<sup>1-7,9-10</sup> in all forms of SCD, with the highest incidences in sickle cell anaemia.<sup>1-3,5-7</sup> Deaths<sup>1-6,8-10</sup> and debilitating neurological sequels to the growing child such as cognition loss, motor and sensory deficits, learning difficulties, psychological and emotional problems as well as seizure disorders have been recorded after the first stroke.<sup>1,6-7,9,11-13</sup>

The aim of this study was to determine the prevalence of strokes amongst our patients with SCD, describe its clinical features, haematocrit levels on admission, radiological brain imaging, neurological deficits, recurrences, effect of management with chronic blood transfusions therapy (CTT), and the outcome of these children. It is hoped that this information will increase the awareness to strokes in SCD, and the use of Trans Cranial Doppler (TCD) ultrasound studies of the cerebral vessels as a primary prevention screening tool for strokes in SCD.<sup>6-7,14</sup> This is important particularly in low resource countries of the world such as ours where TCD studies are not yet a routine standard of care.<sup>11</sup>

## Materials and methods

This is a descriptive retrospective study of children with SCD seen at the paediatric unit of the National Hospital Abuja, a referral center located in the capital city of Nigeria over a 2.5 year period from January 2009 – June 2012. The hospital provides tertiary level health care and receives patients from both its immediate environs and surrounding cities. The paediatric unit of the hospital has facilities for emergency paediatric care, inpatient admissions, newborn care and outpatient specialist clinics; which includes a weekly sickle cell clinic.

All children attending the sickle cell clinic had their haemoglobin genotype determined by cellulose acetate haemoglobin electrophoresis methods carried out by the Haematology unit of the hospital.

Medical notes of children with SCD who had strokes were retrieved from the medical records department and the following information obtained: demographic data, clinical features, packed cell volume (PCV), and radiological brain imaging as at the time of the stroke. Information on long term neurologic deficits (if any), management with chronic blood transfusion therapy (CTT), recurrence of strokes and their outcome was also obtained.

A stroke was defined as an acute neurologic syndrome secondary to occlusion of a cerebral artery or haemorrhage with resultant ischaemia and neurologic signs and symptoms lasting greater than 24 hours.<sup>1</sup> These were infarctive and/or haemorrhagic strokes based on available clinical and neuro imaging studies of Computed Tomographic (CT) scan and/or Magnetic Resonance Imaging (MRI) of the brain.

Children with SCD attending the clinic received a standard of care according to the unit policy. This comprised SCD genetic counseling of the caregivers and child (as was appropriate for age); counseling for immunizations and nutrition, information on how to prevent and identify crises and early management of same; as well as regular growth monitoring, clinical evaluations, PCV assessments, folic acid supplementation and malaria chemo prophylaxis; and additional Pneumococcal and Haemophilus B Influenza immunizations. In addition, they received an information booklet on SCD. There were facilities available for prompt management of illnesses and complications, emergency admissions, blood transfusions, and exchange blood transfusions. The children could be seen at any time at the Emergency Paediatric Unit.

Children with strokes were seen for follow up in the clinic, and after parental counseling offered chronic transfusion therapy (CTT) - blood transfusions on a monthly basis (every 4 weeks). The aim of CTT was to keep the PCV > 30% and the haemoglobin S < 30%,<sup>6</sup> which is a secondary preventive measure for strokes in SCD. We were however unable to routinely assess the Hb S% in them. Packed red blood cell transfusions (haemoglobin genotype AA) were given as required and the volumes determined by the formula [(Desired Hb - Actual Hb) x Weight (kg) x 3], according to the unit policy. Post transfusion PCVs were determined after 48 – 72 hours. The children had their serum iron studies assessed and iron chelating therapy prescribed as required. Hydroxyurea starting at 15mg/kg and increasing to 30mg/kg was given to all the children with strokes after parental counseling. This drug was closely monitored for side effects by 2 monthly complete blood counts, liver and kidney function tests. Other supportive therapy as required for rehabilitation such as physiotherapy, speech therapy, hearing aids, anti convulsant therapy were provided in association with the appropriate specialist departments.

The results were presented as simple frequencies and percentages and shown in tables. Descriptive statistics were expressed as means +/- 2 standard deviations. Statistical evaluations were done by Microsoft Excel 2007 and Statistical Package for Social Sciences SPSS version 16. Associations between variables were done by the chi square test as appropriate. A p value of less than 0.05 was considered as been statistically significant.

## Results

There were 31 children with strokes among the 596 children with SCD seen in the paediatric unit, giving a prevalence of 5.2%. Twenty six (26) case notes were retrieved and the data is presented. There were 12 males and 14 females, M: F ratio of 0.9:1; mean age was 6.4 years (SD 3.4), age range 1 year 7 months – 14 years. The mean duration of follow up was 2.8 years (SD 1.4), range 0.4 – 6 years. The packed cell volumes (PCV) at the time of the strokes ranged from 14 – 29%, with a mean of 21.1% (SD 3.9). The mean expected weight for age according to the modified Wellcome classification was 96.3% with a range of 76.6 – 122%. There were 22 (84.6%) children with normal weight (80 – 120% expected weight for age), and 2 (7.7%) children each with under nutrition (60 - < 80% expected weight for age) and over nutrition (> 120% expected weight for age) respectively. All (100%) the children had Haemoglobin SS (sickle cell anemia) on Haemoglobin electrophoresis. Clinical presentations were: convulsions in 18, inability to use limbs in 11, and weakness of parts of the body in 10, coma in 7 and headaches in 5 children respectively (Table 1). Long term neurological deficits observed during follow up were: hemiplegia and cognition loss 11 children each, aphasia in 8 children, facial nerve palsy in 7 children, and swallowing incoordination in 5 children. Three (3) children had no long term neurological deficits (Table 2).

**Table 1:** Presenting clinical features found in 26 children with SCD and stroke

Presentations n = 26	Frequency (%)
Convulsions	18 (69.2%)
Inability to use limbs	11 (42.3%)
Weakness of limbs	10 (38.5%)
Coma	7 (26.9%)
Headaches	5 (19.2%)
Fever	4 (15.4%)
Inability to talk	3 (11.5%)
Slurred speech	3 (11.5%)
Inability to see	2 (7.7%)
Others	2 (7.7%)

Others 1 (3.8%) each of unsteady gait and dizziness

**Table 2:** Long term neurological deficits in 26 children with SCD and stroke

Long term Neurological deficits n = 26	Frequency (%)
Cognition loss	11 (42.3%)
Hemiplegia	11 (42.3%)
Aphasia	8 (30.8%)
Hemiparesis	8 (30.8%)
Facial nerve palsy	7 (26.9%)
Swallowing incoordination	5 (19.2%)
Seizure disorder	3 (11.5)
Slurred speech	2 (7.7%)
Urinary/Faecal incontinence	2 (7.7%)
Quadriplegia	2 (7.7%)
ADHD	2 (7.7%)
None	3 (11.5%)
Others	3 (11.5%)

Others 1 (3.8%) each of behavioural disorder, learning disability and deafness. ADHD - Attention Deficit Hyperactivity Disorder

There were 17 (65.4%) radiological brain imaging studies done in 16 children; 8 Computed Tomography (CT) Scans, and nine Magnetic Resonance Imagings (MRI) (Table 3). Ten (38.5%) children had no brain imaging study done. The imaging studies were done in the acute phase - first 72 hours and up to a week after the stroke event. These brain imagings showed cerebral atrophy (Fig 1) in 10 children, acute cerebral infarcts (Fig 2) in nine children, chronic cerebral infarcts in six children and intra cranial haemorrhage in one child (Fig 3). The child with the intracranial haemorrhage had the CT scan done 48 hours after the stroke. There were four normal brain imagings. One child had two CT scans of the brain; the initial scan was normal, while the scan obtained after the second stroke three years later was abnormal, showing multiple old and new infarcts.

**Table 3:** Radiological imaging (CT scan and MRI brain) in 16 children with SCD and stroke

CT/MRI brain findings n = 17*	Frequency (%)
Cerebral atrophy	10 (58.8%)
Acute cerebral infarcts	9 (52.9%)
Chronic cerebral infarcts	6 (35.3%)
Acute ischaemic changes	4 (23.5%)
Acute cerebral bleed	1 (5.9%)
Porencephalic cyst	1 (5.9%)
Normal	4 (23.5%)

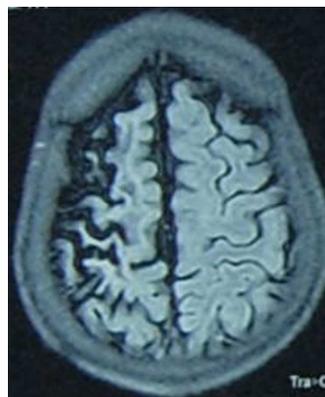
\*One child had 2 CT scans of the brain



**Fig 1**

7 years, male MRI brain: T2 FLAIR MRI brain (Transverse plane)

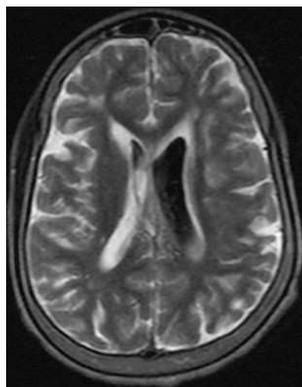
- Wedge shaped area of hypo intensity in the right frontal lobe and prominence of the adjacent cerebral sulci - cerebral infarction
- Prominence of the right Sylvian fissure and inter hemispheric fissure, dilatation of the frontal horn of the right lateral ventricle – porencephalic cyst



**Fig 2**

7 years, male MRI brain: T2 FLAIR MRI brain (Transverse plane)

- T2 weighted MRI of the brain in transverse plane showing cerebral atrophy of the right cerebral hemisphere

**Fig 3**

10 years, female MRI brain: T2 FLAIR MRI brain (Transverse plane)

- Hypo intense areas consistent with intra ventricular bleed/hemorrhage in both bodies of the lateral ventricles worse on the left side;
- Dilatation of the left lateral ventricle with resultant atrophy of the adjacent cerebral cortex

Twelve children (46.2%) children had recurrences of stroke ranging in number from one to four, which occurred from six months to three years after the initial stroke. There were no statistical significant differences between the children with recurrences of stroke compared to those without recurrence regarding the age, sex,

weight, or PCV (Table 4).

Fifteen (57.7%) children were enrolled in a monthly chronic blood transfusion therapy (CTT, hyper transfusion) programme, a standard of care for children with SCD who have had strokes<sup>6</sup>, while 11 children (42.3%) were not (Table 4). These transfusions had been given for a period of four months to three years, eight months at the time of writing. Of the seven children with regular blood transfusions, five (71.4%) had no recurrence of stroke while two (28.6%) did. Four (66.7%) of six children on irregular CTT as well as five of the 11 (45.4%) children not on blood transfusions had recurrences of strokes. These differences were not statistically significant  $p > 0.05$  (Table 4). Two children – an 11 year old girl and a 10 year old boy stopped the transfusions after 8 months and one year, five months respectively. The girl had a recurrence of stroke after three years, while the boy did not have a recurrence of stroke in 4 years of follow up.

**Table 4:** Demographic features, PCV values, effect of chronic transfusion therapy, and outcomes on recurrence of stroke in 26 children with SCD

	Recurrence of stroke Yes	Recurrence of stroke No	Chi square $X^2$	Degree of freedom df	P value
<i>Age (years)</i>					
1 - < 5	5	4	0.503	2	0.78
5 - < 10	4	6			
10 - < 15	3	4			
<i>% weight for age</i>					
80 – 120%	9	13			
60 – 80%	1	1	2.59	2	0.27
80 - 120%	2	0			
<i>PCV (%)</i>					
< 15%	1	1			
15 - < 20%	2	2	4.57	4	0.34
20 - < 25%	8	5			
25 - < 30%	1	3			
Unknown PCV <sup>a</sup>	0	3			
<i>Sex</i>					
Male	5	7			
Female	7	7	0.18	1	0.67
<i>CTT</i>					
Regular CTT	2	5	1.89	2	0.38
Irregular CTT	4	2			
Stopped CTT	1	1			
<i>Outcome</i>					
Lost to follow up	3	4	2.06	3	0.56
Alive	8	9			
Dead	1	0			
Referred to other hospital	0	1			

2 children commenced blood transfusion therapy after the 2<sup>nd</sup> stroke

<sup>a</sup>The children with the unknown PCV at the time of stroke had been transfused prior to arrival at the hospital

CTT – Chronic transfusion therapy: - Regular: Monthly blood transfusions as required; Stopped: No blood transfusions for more than 4 consecutive months; Irregular: Irregular blood transfusions but not for up to 4 consecutive months in between transfusions

Regarding outcome at the time of writing, 17 (65.4%) of the children were alive, 7 (26.9%) were lost to follow up, 1 had died, while 1 was referred to another centre (Table 4). The 17 children who are alive are being followed up in our clinic and are receiving, in addition to standard care for SCD offered at our center, rehabilitation by physiotherapy, speech therapy, hearing aids, and other medications such as anti-convulsants as required. Two children attend special schools for the mentally handicapped and for children with special needs respectively. Another child was taken out of regular school due to persistently poor performance, and a 4<sup>th</sup>

child who is wheel chair bound attends a regular school. An 8 year old girl died during a recurrent stroke episode at the hospital, while the referral was due to relocation of the family.

## Discussion

The 5.2% prevalence of strokes amongst our patients with SCD is higher than 4.01% reported from the Cooperative Study of Sickle Cell Disease (CSSD),<sup>1</sup> though

lower than previous reports of 7.8% from the Jamaican cohort study of SCD,<sup>2</sup> and 11.5% reported from the Dallas cohort study of SCD.<sup>5</sup> It is however similar to recent previous reports of up to 5.4% from Nigeria by Ahmed<sup>8</sup> and Fatunde<sup>9</sup> though much higher than <1% previously reported by Izuorah<sup>11</sup> and Akinyanju<sup>15</sup> 3 decades earlier. All the children had sickle cell anaemia and the age range was similar to previous reports with majority of the children being below 10 years of age.<sup>1-5</sup> Low steady state haemoglobin concentration and acute decreases in the steady state haematocrit have been identified as risk factors for strokes in SCD.<sup>1,2,6,7,14</sup> About a quarter of the children of this study had PCV of less than 25% at the time of the stroke. The significance of this finding as a possible risk factor for stroke in this study could not be ascertained. We were not privy to the steady state haematocrit levels of the children and could therefore not determine if this represented acute decreases in steady state haematocrit or not. This was a limitation of the study.

The clinical features at time of stroke such as convulsions, weakness of parts of the body, inability to use the limbs, headaches and coma have been previously reported as are the varying long term neurological deficits of hemiplegia, aphasia and facial nerve palsy recorded in this study.<sup>2,3,6-9,11-13,16</sup> While these manifestations are in consonance with most previous studies,<sup>6-7,11,13,16</sup> a striking feature in the present study is the cognition loss in over 50% of the patients. Severe deficits like quadriplegia, deafness and swallowing in-coordination were also among those observed. These have enormous significance, emphasizing the loss of the ability of these children to attain their true potentials and live a normal quality of life. The need for particular investigations such as radiological brain imagings, and various forms of rehabilitation including physiotherapy, special schools, special care givers, medications, speech therapy and hearing aids increases the cost of care of these children and constitute a burden to the family and society. Of note are the three children with clinical and radiological features of strokes, and no long term neurological deficit. Such occurrences have been previously reported in literature.<sup>1,6-7,13</sup> Associations of the location and volume of anatomical sites of CNS infarcts with specific areas of neurocognitive dysfunction have been described by Kirkham, Schatz and others, in defining the type and magnitude of neurological sequelae in stroke.<sup>6-7,17-18</sup> Thus, when the site of the cerebral infarcts occurs in non motor areas of the brain, there may be minimal or no motor deficits, although subtle neuro cognitive dysfunctions may appear in the future.<sup>7,17,18</sup>

It was not possible to have radiological imagings for all the children in the study. This was due to the cost of the investigations which could not be afforded by some of the care givers. This highlights the need for health insurance in low resource countries with wide spread poverty or appropriate increase in government funding to cater for the health needs of her people. The findings from radiological imaging done at the time of stroke among our patients were similar to those reported from the

CSSD and other studies,<sup>1,6-7,19-22</sup> with infarctive strokes occurring more commonly than haemorrhagic strokes. We were unable to do magnetic resonance angiography or other arteriogram as was done in these studies just alluded to, which would have yielded further information. Cerebral haemorrhages are uncommon in children with SCD during a stroke<sup>1,6-7</sup> and only one of the children who had brain imaging in this study had this feature, similar to the CSSD.<sup>1</sup> It is also noteworthy that four children in this study had normal brain imagings despite the clinical features of strokes. It is likely that in these children so referred to, the investigations were done quite early in the course of the stroke before the radiological changes could be recorded by the brain imaging techniques available at the hospital. It has been documented that CT scans may not show abnormalities within the first 24 hours of a stroke, whereas diffusion-weighted and T2 weighted MRI may show ischaemic changes and haemorrhages within the immediate 1 - 3 hours of the event.<sup>6-7,20-22</sup> We also had children with brain imagings done during the acute stroke event that showed evidence of chronic cerebral infarcts, thus strengthening the suggestion of previous silent infarcts (brain infarction on imaging studies in the absence of neurologic symptoms).<sup>1,6-7,21-22</sup> This underscores the importance of Trans Cranial Doppler (TCD) studies of the cerebral vessels as a screening tool to identify children with SCD at high risk of stroke and commence therapy for primary prevention of strokes.<sup>6-7,14</sup> This therapy comprises regular blood transfusions intended to reduce the Hb S concentration to < 30% when there are abnormally high blood flow velocities of the cerebral arteries on TCD studies. This recommendation is based on the results of the Stroke Prevention Trial in Sickle Cell Anaemia (STOP)<sup>14</sup> study that showed a clear benefit for prophylactic transfusions in preventing stroke in these children.<sup>6,7</sup>

Strokes in children with SCD have been reported to recur in up to 14% of cases in developed countries, while in developing countries the recurrence of 61% is much higher.<sup>1,3,5,6,7,9</sup> We had a recurrence rate of 42%, which was higher than has been previously reported for developed countries, but similar to studies from Nigeria and other developing countries.<sup>1,3,5-7,9</sup> The difference in recurrence rates between the developed and developing countries could be attributed to better health care in the developed countries of the world and the use of the hyper transfusion programmes, which is not done routinely in most developing countries.<sup>11</sup> It has also been suggested that there might be some genetic or environmental factors responsible for this difference.<sup>6,7,24</sup>

Chronic Transfusion Therapy CTT (hyper transfusion programs) to keep the PCV > 30% and the Hb S concentration < 30% are the standard of care to prevent secondary recurrence of strokes in SCD, reducing the risk from approximately 67% to less than 10%.<sup>6-7</sup> Some caregivers in the present study refused this form of treatment despite counseling. We had difficulties maintaining the blood transfusions over the period of this report, as well as managing the ensuing complications that

arose, such as non availability of blood as required, transfusion related costs and iron overload. Majority (71.4%) of the children receiving CTT in this study did not have recurrence of strokes; in comparison to about 45% of the children who never received these transfusions that had stroke recurrences. These findings are similar to what was reported by Adams<sup>6</sup> and Kirkland.<sup>7</sup> The recurrence of strokes despite regular blood transfusions in SCD as found in this study have been previously reported.<sup>6, 7, and 24</sup> It was suggested that although chronic transfusions can reduce the risk of having a recurrence of stroke, it cannot completely eliminate it.<sup>6</sup> Moyamoya disease, the formation of a mass of small friable blood vessels in response to severe stenosis or occlusion of major intracranial vessels, frequently seen in SCD, has been identified as a risk factor for stroke recurrence despite regular transfusion.<sup>6, 7, 24 - 25</sup> These blood vessels, which have a propensity to rupture, may be responsible for the occurrence of frequent strokes. Indeed, recurrent infarctions have been reported to be more likely to occur in children with moyamoya syndrome.<sup>7</sup> Furthermore, we had one child who stopped CTT, as well as the 6 children who never had CTT who had no recurrence of strokes in the follow up period. These children, who were not on CTT, had been receiving the drug hydroxyurea. Similar experiences have been documented elsewhere<sup>6,7,26</sup> and indeed hydroxyurea has been suggested as an alternative treatment to

CTT in the secondary prevention of strokes in SCD.<sup>6,7</sup> Despite the fact that the small sample size in this study makes any definitive statement about usefulness of CTT (hyper transfusion programme) difficult, it does seem to have been beneficial in preventing recurrence of strokes in these SCD patients.

## Conclusion

We found that strokes occur with a prevalence of 5.2% and constitute an important cause of morbidity in SCD patients in Abuja, Nigeria, with convulsions being the commonest presenting feature and hemiplegia and cognition loss the most commonly encountered long term neurological deficits. It was also noted that chronic transfusion therapy (hyper transfusion programme) did seem beneficial in preventing stroke recurrences in these patients. It is advocated that primary prevention of strokes by Transcranial Doppler studies of the cerebral arteries<sup>14</sup> as a screening tool be done on regular basis in children with SCD so as to initiate preventive measures as deemed appropriate.

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