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Stroke in Nigerian children with sickle cell disease

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Summary
We reviewed our records over a 15-year period to determine whether or not the impression that stroke complicating sickle cell disease was less common than reported in North America. Records of children aged 16 years and below with a diagnosis of stroke seen at the University College Hospital, Ibadan, Nigeria between 1988 and 2002 were examined. Thirty-nine such patients were identified but only 31 had detailed records available for study. Twenty-seven of these had sickle cell disease, 26 with haemoglobin genotype SS and 1 with Hb S+C. Sickle cell disease was therefore responsible for 87% of stroke seen in children at our centre. With an average clinic population of about 500 patients with sickle cell disease, the hospital frequency of stroke among these patients is estimated at 5.4%. The mean age of occurrence of the first stroke was 6.8 years ranging from 17 months to 11 years. Of the 7 patients who had CT scans of the brain done, 5 had evidence of cerebral infarction while 2 had intracerebral haemorrhage. While only 2 deaths occurred among the cases reviewed, morbidity was significant with only 6 patients achieving complete recovery. Recurrent stroke occurred after an average of 25.6 months in 8 of 13 patients who were followed up (61.5%). The incidence of stroke among African children with sickle cell disease appears to be not as high as reported in patients from North America.

Keywords: *Stroke, sickle cell disease, Nigerian children.*

Résumé
Nous avons révu nos régistres depuis 15 ans pour déterminer si l'impression que le blocage cerebral complicant la drépanocytose était moins commun que reportée en Amerique du Nord. Les régistres d'enfants agés de moins de 16 ans diagnostiqués ayant le stroke étaient examinés au Centre Universitaire Hospitalier d'Ibadan, Nigéria entre 1988-2002. Sur trente neuf patients étaient identifies, 31 seulement avaient un registre detailés. Vingt-sept étaient drépanocytaire, 26 ayant le genotype de l' hémoglobine SS et un Hb s+c. la drépanocytose était responsible de 87% de stroke vu chez ces enfants. Avec une population moyenne a la clinique de 500 patients drépanocytaire, la frequence du stroke a l'hopital était estimée a 5.4%. La moyenne d'age de la premiére stroke était de 6-8 ans variant entre 1.7 - 11 ans. Sur les 7 patients qui avaient fait un scanner du cerveau, 5 avaient d 'incidence d'infraction cerebral alors que 2 patients avaient l'hémorrhagie intracérebrale. Cependant seulement 2 décés parmi les cas révus, la morbidité était significative avec seulement 6 patients ayant eu une guérrisson compléte. La recurrence du blockage cérebrale après 25.6 mois était observée chez 61.5% patients suivi. L'incidence du blocage cérebrale parmi les enfants Africain drépanocytaire apparait être moins elevée comparée aux patients d'Amérique du Nord.

Introduction

Nigeria with a population of more than 100 million people and an incidence of sickle cell disease (SCD) of 1-3% possibly has the largest population in the world of people with sickle cell disease [1]. However, local reports of stroke, a not uncommon complication of the disease, especially in children, are scanty. One such report is that of Adeloye *et al* [2] who reported a hospital incidence of 4%. This has caused speculation that stroke may be less common among SCD patients in Africa compared with those in Jamaica and United States of America. The incidence of stroke among these patients in USA was variously quoted as 13 to 17%, the relative risk of developing stroke being about 0.002 [3-5]. However, more recent estimates of stroke in SCD of 7-8% [6] are less than those of previous reports. While community studies would best address the incidence of stroke among our patients with SCD, these are not yet available. However, an idea of the occurrence of this complication may be obtained from hospital records since the majority of patients with SCD visit one health facility or another at some time in their lives.

Patients and methods

The records of all patients aged 16 years and below with a diagnosis of stroke admitted to the paediatric wards or seen in the children's outpatient clinic of the University College Hospital, Ibadan, Nigeria between January 1988 and December 2002 were examined. The biographical data, mode of presentation, haemoglobin type, course of the disease and sequelae in these patients were noted. There were two groups of patients. The first were those admitted to the hospital on account of presentation shortly after the episode of cerebrovascular accident. The other group consisted of patients seen in the outpatient clinic who presented as cold cases several weeks to months after the sudden neurological catastrophe.

Results

During the 15 year period under review, the diagnosis of cerebrovascular accident (CVA) was made in 39 children who were admitted to the children's wards or seen in the children's outpatient clinic. Of these, records were avail-

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able for detailed study in 31 patients. Twenty-seven of these patients had sickle cell disease; 26 with Hb SS and 1 with Hb S+C. Sickle cell disease therefore accounted for 87% of the cases of stroke in Nigerian children in this review. Of the patients with SCD, ten were male while 17 were female giving a male: female ratio of 1:1.7. As the average number of patients with sickle cell disease attending our clinics at this time was about 500, the hospital frequency of CVA is 5.4%. The children came from all the different socio-economic groups of the community as determined by parents' income and education using the formula devised by Oyedeji [7]. The number of patients from each of the 5 (1 to 5) socio-economic groups were 5,7, 9, 3, 3 respectively.

The age of occurrence of a first stroke ranged from 17 months to 11 years with a mean (SD) of 6.8 (3.7) years. Sixteen of the patients presented in the emergency ward as acute cases shortly after the episode of stroke while 11 patients were seen in the clinic as cold cases with residual paralysis several weeks to months after the acute illness that had led to the paralysis.

Table 1: Clinical presentation of stroke in 27 children with sickle cell disease.

Presenting features*	No. of patients (%)
Hemiparesis	20 (74.1)
Quari paresis	1 (3.7)
Aphasia	12 (44.4)
Coma	11 (40.7)
Cranial nerve palsies	9 (33.3)
Seizures	9 (33.3)

**Some patients had more than 1 of the above presentation*

Table 1 shows the clinical presentation of the 27 patients at first presentation. As expected, the majority 20 (74.1%) presented with hemiparesis; aphasia was common, occurring in 12 patients (44.4%) while cranial nerve palsies were also prominent presenting features. The commonest cranial nerve involved was the seventh nerve, being affected in 8 of the 9 cases. Only 7 patients seen in the years of the study period when a CT scanner was available in the hospital had brain CT scan done. Of these, 5 patients had evidence of infarction, while two had evidence of intracerebral haemorrhage. Infarction therefore occurred in 71.4% of the cases that had CT scan examination. Three patients had blood stained cerebrospinal fluid (CSF) following non-traumatic lumbar puncture, one of these patients had a post mortem examination following death, which showed subarachnoid haemorrhage over the left cerebral hemisphere.

Associated clinical conditions in patients presenting in the acute phase included severe hypertension in 3 cases. These children were aged 9, 11 and 12 years. Renal function in each of them was normal and each required several weeks of anti-hypertensive therapy to control the blood pressure. Other associated conditions included *Klebsiella* osteomyelitis in one case, pyogenic meningitis in another case and lobar pneumonia with pleural effusion in a third patient. Two patients had associated vaso-occlussive crises.

Morbidity was considerable, the mean (SD) number of days of admission being 19.9 (21.7) days ranging from 2 to 56 days. Two of the 16 patients presenting in the acute phase died giving a case fatality rate of 12.5%. Both patients died within 12 hours of presentation and clinical diagnosis was that of intracranial haemorrhage in both patients. One of them had an autopsy examination, which showed subarachnoid haemorrhage over the left cerebral hemisphere. Over a period of follow up ranging from 3 months to 9 years (mean 27.6 months), 13 of 25 surviving patients (52%) were seen in the clinic, others being lost to follow-up. Eight of these 13 patients (61.5%) had recurrent episodes of cerebrovascular accident. Number of recurrences ranged from 1 to 5. The interval from the first episode to the first recurrence varied from 12 to 42 months (mean 25.6 months).

Table 2 shows the long term sequelae or the residual defects on discharge in the 25 surviving patients. Only 6 of the 25 surviving patients (24%) made complete recovery. Of the 19 patients with residual hemiplegia, 10 had paralysis of the left side and 9 were affected on the right. One patient died of acute chest syndrome 3 years after the CVA while another died six years later of severe anaemia.

Table 2: Sequelae of stroke in 25 children with sickle cell diseases who survived initial stroke

Sequelae*	No. of patients (%)
Paresis (hemi/quadri)	19 (76)
Seizure disorder	6 (24)
Aphasia	2 (8)
Dysphasia	1 (4)
Mental retardation	2 (8)
Complete recovery	6 (24)

**Some patients had nore than one sequelae*

Discussion

The diagnosis of cerebrovascular accident in children with sickle cell disease in this review was based on presentation of patients with acute onset of focal brain dysfunction usually manifested as hemiplegia and/or cranial nerve palsies with or without other neurological symptoms such as seizures and impairment of consciousness. Bloodstained CSF and characteristic findings on CT scan of the brain confirmed diagnosis in some cases. The "cold" cases were diagnosed based on the presence of hemiplegia which was reported to have occurred during a previous acute illness. Our review confirms some previously noted facts. Sickle

cell disease is the commonest cause of stroke among black African children as it is in black American children [5] being the aetiology of stroke in 87% of childhood cases in this study. Infarction is the commoner pathological event in these children [5] and mortality may be minimal in cases of infarction [8]. The mean age of occurrence of the first episode of stroke in this review of 6.8 years agrees well with figures of 6 to 8 years recorded by others [4,9,10]. Standard management of these acute cases at our centre consisted of blood transfusion (packed red cell transfusion or partial exchange blood transfusion), intravenous fluids, oxygen by face mask, antibiotics and/or anti-convulsant drugs as required.

The incidence of stroke among patients with SCD in North America has been variously quoted as 7 to 17%. The figure frequently quoted for African patients is that of Adeloye *et al* [2] who reported an incidence of 4% among 257 patients (children and adults) presenting at the University College Hospital, Ibadan in 1970. Some workers have wondered if this figure is an under-estimate being a reflection of a higher mortality rate among affected African children thus reducing the number of patients at risk for development of acute stroke [10]. This review gives a higher figure than the previous one. This may be due to the fact that the current review involves only children in whom CVA is more prevalent than in adults who were included in the Adeloye study [2].

The relatively low case fatality rate recorded in this study is noted, the 2 death occurring in patients with intracranial haemorrhage. Coma is supposed to be a sign of poor prognosis in these patients [10], but only 2 of the 11 patients presenting in coma died. The reason for this favourable prognosis among our patients is not clear. It may be that some children who developed deep coma secondary to stroke who would have died in hospital, died at home and were not brought to the hospital at all. A significant finding is the occurrence of severe hypertension in 3 patients with CVA. It has been reported that intracranial haemorrhage may be associated with hypertension [11]. As we do not routinely check the blood pressure of children in the clinic, it is not clear if any of the affected children had been hypertensive before the occurrence of the CVA. Whether the high blood pressure is a cause or effect of the CVA is not clear. Since these 3 children were relatively young, it may be wise to routinely check blood pressure in all children with sickle cell disease. Akpede *et al* [12] reported 2 cases of acute encephalopathy with hypertension and Gram negative sepsis in children with sickle cell disease aged 8 and 11 years. Brain CT scans were not done in either of the 2 patients but it is conceivable that, similar to the presentation in 3 of the patients in this series, CVA may have contributed to the acute encephalopathy in these patients. Pegelow *et al* [13] documented lower blood pressures in patients with sickle cell disease when compared with published means for age, race and sex. However, the risk for occlusive stroke increased with systolic but not diastolic pressure. It would be advisable if routine blood pressure measurements could be taken in children with sickle cell disease, if not in all children.

Although, mortality is only 12.5% in this review, morbidity is considerable since only 24% of the surviving patients made complete recovery. This agrees with findings of other authors that permanent deficit following stroke among children with sickle cell disease is quite common [9]. It is notable that although aphasia and cranial nerve palsies are relatively common presenting complaints, these tend to disappear with time and are not prominent long-term sequelae. Of greater concern is the propensity for recurrent strokes, estimated at 60- 90% [9,10,14] and reported to occur at a median interval of 19 months after the first stroke [9]. Follow up among our patients is poor, but 61.5% of the patients followed up for an average of 27.6 months developed recurrent strokes after an average of 25.6 months.

Hypertransfusion regimen is well documented to reduce recurrent strokes in children with sickle cell disease [15,16]. However, we do not have the facilities to give blood transfusions every 3 to 4 weeks as would be required by this kind of intervention. In addition, we do not have the facility to deal with the complications of hypertransfusion regimen such as development of haemosiderosis and allo-immunnisation. Increasing the haemoglobin F level in the blood of these patients by the administration of Hydroxyurea is said to lead to amelioration of disease severity in patients with SCD [17] and has been shown to reduce the tendency of recurrent strokes [18,19]. We are in the process of offering this therapy to some of our affected patients. The ultimate goal would be to identify susceptible patients before development of the first stroke and take steps to prevent this initial event. This has been successfully carried out in one study in North America [20]. It is hoped that further research may help in developing simple methods of identifying patients at risk of development of a first stroke as it has been shown that brain infarcts and vasculopathy of major brain vessels may occur in young children with sickle cell disease in the absence of clinical stroke [21]. Appropriate preventive measures taken early may avert this crippling complication of sickle cell disease.

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