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Neurological complications of sickle cell disease in children in Yaoundé (Cameroon)

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Abstract

Introduction: Sickle cell disease, the most common genetic disorder in Cameroon, is fraught with neurological complications, the prevalence of which is unknown in children. The aim of our study was to evaluate the neurological complications of this condition in children. Methods: We conducted a retrospective study of children with sickle cell disease aged less than 15 years over a 7-year period from January 1, 2015 to December 31, 2021 in three university hospitals in the city of Yaoundé. Data collected were presented as mean ± standard deviation, frequencies and percentages. Results: Among the 3,437 sickle-cell cases received in these three hospitals, we collected 70 patients with neurological complications, representing a frequency of 2%. Their mean age was 7.1 ± 3 years, and they were predominantly male (55.7%). Twenty-five patients (35.7%) had no follow-up and 14 (20%) were on hydroxycarbamide. Vaccination status was not up to date for age in 80% of cases. Neurological complications included stroke (78.6%), epilepsy (14.3%), meningitis (12.9%) and brain abscess (5.7%). Sequelae observed in children with neurological complications were: motor deficit, aphasia and blindness. Mortality was 10%. Conclusion: In our context, neurological complications of sickle cell disease frequently occur around the age of 7. They are mainly cerebrovascular and infectious. Reinforcing preventive measures such as neonatal screening, vaccination, antibiotic prophylaxis, regular trans-cranial echodoppler monitoring and improved access to hydroxycarbamide would help reduce their frequency.

Keywords: Sickle cell disease, Neurological complications, Genetic disorder.

INTRODUCTION

Sickle cell disease (SCD) is the most common genetic disorder in the world. Of the 20 to 25 million people living with sickle cell disease worldwide, 12 to 15 million live in sub-Saharan Africa and die before the age of 5 [1,2]. A study carried out in Cameroon on 5,856 newborns screened at birth revealed a prevalence of the AS trait of 13.2% and that of the SS homozygous form of the disease of 0.1% [3].

Stroke, conditional and abnormal cerebral blood flow, seizures and headache were the most frequently reported complications in Africa, with overall prevalence rates of 4.2%, 10.6%, 6.1%, 4.4% and 18.9%, respectively [4]. In Cameroon, Njamnshi et al. reported that the prevalence of stroke was 6.67% in the general population [5], while Obama et al in 1994 reported that sickle cell anaemia was the main aetiological factor in stroke (31.4%) in children [6].

Despite the resolution adopted by the 63rd session of the United Nations General Assembly, which recognised SCD as a public health problem [4], little data is available in Cameroon on the neurological complications of sickle cell disease in children, which is why we conducted a study to assess these complications.

MATERIAL AND METHODS

We conducted a descriptive cross-sectional study with retrospective data collection over a seven-year period, from 1 January 2015 to 31 December 2021. This was a multicentre study conducted in the paediatric wards of three university hospitals providing follow-up for children with sickle cell disease in the city of Yaoundé, Cameroon: the Chantal Biya Foundation Mother and Child Centre, the Yaoundé Gynaecological-Obstetric and Paediatric Hospital and the Yaoundé University Hospital Centre.

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Sampling was consecutive and non-probability. Recruitment targeted homozygous sickle cell children aged 0 to 15 years followed up in these hospitals. Patients with a neurological condition of aetiology other than SCD, in particular sequelae of neonatal asphyxia, ketoacidosis coma or head trauma, and those whose medical records could not be retrieved, were excluded from our study. Data collected included age, sex, reason for admission, circumstances of discovery of sickle cell disease, follow-up, prophylaxis (vaccination status, hydroxyurea, antibiotic prophylaxis); clinical variables; paraclinical data: cerebral computed tomography (CT), cerebral MRI, transcranial echo-doppler, electroencephalogram, cytobacteriological examination of cerebrospinal fluid; course (complete remission, sequelae, death).

Data were entered and analysed using SPSS version 23 software. Central tendency parameters (mean) and/or dispersion parameters (standard deviation, maximum, minimum) were used to describe continuous variables. Categorical variables were described in terms of mean ± standard deviation, percentage and frequency. The chi-square test was used to describe associations between variables, with a significance threshold of $p<0.05$.

Ethical clearance was obtained from the Institutional Ethics Committee for Human Research of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I, as well as research authorisations from the administrative managers of the Chantal Biya Foundation Mother and Child Centre (AUTORISATION DE RECHERCHE), the Yaoundé Gynaecological-Obstetric and Paediatric Hospital (AUTORISATION N°214/CIERSH/DM/2022) and the Yaoundé University Hospital Centre (N°066/AR/CHUY/DG/DGA/CAPRC).

RESULTS

During our study period, we consulted 3437 records of children with SCD. A total of 70 patients presenting with a neurological complication were retained, representing a hospital incidence of 2%. Of these, 39 were male (55.7%), giving a sex ratio of 1.3. The average age of these children was 7.16 ± 3 years, with a minimum of 2 years and a maximum of 14 years. The 6-10 age group was the most represented, at 58.6%. Twelve children did not attend school. (Table 1)

SCD was mostly discovered after the age of 2, in 67.1% of cases, in particular as a result of vaso-occlusive crises (25.7%) and stroke (21.4%). Forty-five patients (64.3%) were monitored, 35 of them regularly (50%). Of these patients, 14 were receiving hydroxyurea (20%) and 25 antibiotic prophylaxis (35.7%). Immunisation status was not up to date in 80% of patients. (Table 2)

The main acute neurological signs and symptoms were: motor deficit (60/70 or 85.7%), aphasia (33/70 or 47.1%), coma (34/70 or 48.6%) and convulsions (33/70 or 41.7%).

Some patients presented with two neurological complications simultaneously. Stroke was the most common neurological complication (78.6%), followed by epilepsy (14.3%). In terms of functional prognosis, 83.6% of patients with stroke retained motor difficulties or deficits as an after-effect. There was a significant association between the diagnoses of stroke and meningitis and the occurrence of sequelae. (Table 3)

Of the 55 cases of suspected stroke (55/70, i.e. 78.6%), meningitis was the primary diagnosis in 15 patients, and 17 patients did not have a brain scan. We noted 30 cases of ischaemic stroke (30/38 or 78.9%), 5 cases of haemorrhagic stroke (5/38 or 13.1%) and in 3 patients the cerebral scanner was normal (7.9%). The territory most affected was that of the middle cerebral artery, with a frequency of 91.4% (n=32/35), followed by the posterior cerebral artery (n=2/35) and the posterior cerebellar artery (n=1/35). Stroke recurrence occurred in 15 patients (27.3%).

At the end of hospitalisation, 53 patients (75.7%) had at least one sequela. The mortality rate was 10%. Of the haemorrhagic strokes recorded, 40% died during hospitalisation (n=2). The main sequelae were motor deficit and aphasia (Table 4).

Table 1: Distribution of patients by age and sex

	Number (n)	Percentage (%)
Age range (years)		
0-5	19	27,1
6-10	41	58,6
11-15	10	14,3
Sex		
Male	39	55,7
Female	31	44,3
Out of school	12	17,1

Table 2: Distribution of patients by medical history

Variables	Numbers (n)	Percent (%)
Age of discovery		
< 2 years	23	32,9
≥ 2 years	47	67,1
Circumstances of discovery		
Vaso-occlusive crisis	18	25,7
Anaemia	11	15,7
Dactylitis	13	18,5
Screening	2	2,9
Cerebrovascular accident	15	21,4
Other	11	15,7
Follow-up		
Yes	45	64,3
No	25	35,7
Folic acid	45	64,3
Hydroxyurea	14	20
Penicillin prophylaxis	25	35,7
Up-to-date vaccination status	56	80

Table 3: Neurological complications and prognosis

Neurological complications	Sequelae	Complete remission	p-value
Stroke	46 (83,6 %)	9 (16,4 %)	0,003
Epilepsy	6 (60 %)	4 (40 %)	0,211
Meningitis	4 (44,4 %)	5 (55,6 %)	0,019
Brain abscess	1 (25 %)	3 (75 %)	0,973

Table 4: Distribution of patients by outcome

Prognosis	Numbers (n)	Percent (%)
Death	7	10
Complete Remission	10	14,3
Remission with sequelae	53	75,7
Motor deficit	51	72,9
Aphasia	20	28,6
Facial palsy	2	2,9
Blindness	1	1,4

DISCUSSION

This study provides data on the neurological complications of sickle cell disease in children in Cameroon.

Neurological complications of sickle cell disease in children were common. Stroke, epilepsy and central nervous system infections (meningitis and brain abscesses) were the most common complications. The main acute neurological signs and symptoms were motor deficit, aphasia, coma and convulsions, as reported by Kirkham et al. in 2021 [7].

The incidence of neurological complications in sickle cell patients in our study was 2%, whereas other authors such as Talha et al. in Sudan found an incidence of 10.6% [8]. This difference could be explained by the fact that the data were collected retrospectively, and we did not include clinical manifestations such as headaches and cognitive disorders.

The search for certain complications such as silent cerebral infarctions, peripheral neuropathies, neurocognitive deficits and Moyamoya disease is difficult in the Cameroonian context because of the unavailability and high cost of specific diagnostic tests (cerebral MRI, transcranial Doppler ultrasound, electroencephalogram and neuropsychological evaluation), as reported in a recent review of these complications in sickle cell patients [4].

In two-thirds of the children in our study, sickle cell disease was discovered after the age of 24 months, which was similar to the work of Akodu et al in Nigeria, who found an average age of 27.3 months [9]. In our study, 21.4% of patients had a stroke [3,10,11]. Just over a quarter of children presented with a neurological complication before the age of 6 years, the youngest in our cohort being two years old, which is similar to the findings of Ndiaye et al who found an average age of 6.7 years [12]. It has been described that the later a child is diagnosed with sickle cell disease, the higher the incidence of stroke. In view of the early onset of these acute complications, early neonatal screening would enable a comprehensive care approach to be implemented, including prophylactic treatment, parental education, psychological care starting as early as 2 months of age, and the implementation of a follow-up programme to screen for these complications, with the aim of significantly improving mortality and morbidity [2,11,13].

In addition, children with SCD may present with central nervous system infections such as meningitis and bacterial brain abscess, which was the case in 12.9% of patients in our study [7]. The incidence of central nervous system infections has fallen thanks to penicillin prophylaxis and vaccination, increasing the survival rate to the age of 18 to 94% in the United States and 99% in the United Kingdom [2]. However, these preventive strategies are not always available in Africa and, like other authors, we found low prophylaxis rates with only a third of our patients receiving antibiotic prophylaxis and 80% whose vaccination status was not up to date [3,7,8,10,14]. Long-standing epidemiological data have shown that, in the absence of prophylactic measures, the relative risk of bacterial meningitis is multiplied by 300 in children with SCD [1]. The effectiveness of the antibiotic used for prophylaxis will have to take into account our bacterial ecology because, unlike in the West, the germs most frequently found during septicaemia are not pneumococcus but salmonella, staphylococci and klebsiella [2,10,15].

Apart from central nervous system infections, we found that 1 in 7 (14.3%) children with sickle cell disease had epilepsy and 47.1% had convulsions on admission, the aetiological factors of which could be meningitis and all the other causes of febrile convulsions, with malaria in first place, followed by respiratory infections, as highlighted by a Nigerian cohort [7,16]. In a Jamaican series, epilepsy in patients with SCD was 2 to 3 times more frequent than in the general population; in addition, stroke and meningitis were associated with an increased risk of epilepsy in these patients [17]. In a meta-analysis of studies carried out in Africa, the prevalence of convulsions was 4.4% [4].

Nearly half the patients presented with a coma. Kirkham et al. reported that the causes of coma in sickle cell patients were intracranial haemorrhage, extensive middle cerebral artery infarction with oedema and midline displacement (the area most frequently affected in our study), posterior reversible encephalopathy syndrome and venous sinus thrombosis [7].

The prevalence of stroke in sickle cell disease in Africa is just 4.2%. Stroke was the main neurological complication in our study (78.6%), which was similar to other studies [5,6]. However, our frequency was higher than that reported by some authors. This difference could be linked to an underestimation of sub-clinical or frustrating forms which would go unnoticed due to a lack of appropriate means of investigation. Indeed, children with SCD are 250 times more likely to have a stroke than children in the general population [2].

Ischaemic strokes were the most common, most often involving the middle cerebral artery. They are most common between the ages of 2 and 10, with a peak between the ages of 2 and 5 [7]. Hemiparesis was the typical presentation, and in the absence of secondary prevention, recurrence could occur, as was the case in our study in 2 out of 10 children, and in 60 to 92% of cases, according to Kirkham et al [7]. This high rate of stroke and recurrence could be explained on the one hand by the low rate of hydroxyurea use found in our patients, which was similar to other studies [3], and on the other hand by the absence or inadequacy of screening for sickle cell anaemia children at risk of stroke using transcranial Doppler velocimetry, combined with chronic transfusion treatment, helped to reduce the prevalence of stroke from 11% to 1% in Chou et al [7]. In the medium term, recurrent strokes should be prevented by a monthly transfusion programme with the aim of achieving a haemoglobin S level of less than 30% [1].

We reported few cases of haemorrhagic stroke in our series, which is similar to the findings of other authors, but with a high mortality rate (40%). It has been described that the incidence of haemorrhagic stroke increases with age, whereas the incidence of ischaemic stroke decreases [7]. The average age of presentation is higher for haemorrhagic stroke than for ischaemic stroke in children [7].

One sixth of our patients did not attend school. This can be explained by the after-effects of these neurological complications, in particular aphasia, motor deficit or epilepsy, which is a socio-cultural problem in our context [18]. Indeed, it has been reported that children who did not receive hydroxyurea were more likely to drop out of school and to have moderate to severe motor disabilities requiring the assistance of a carer for daily life, as was the case in our study [7]. In addition, a Cameroonian study showed that 37.5% of children with SCD had mild to severe cognitive difficulties, which can also be a disruptive factor in schooling [19]. The severity of SCD, with its frequent and intense vaso-occlusive crises, episodes of anaemic decompensation requiring blood transfusions and severe infections, is often the cause of repeated and more or less prolonged stays in hospital, which can lead to children with the disease dropping out of school.

In our study, three-quarters of patients had a neurological sequela at the end of their hospital stay, and the mortality rate was 1 in 10, which was similar to a Californian study in which 5% of sickle cell children hospitalised for a first or recurrent stroke died [20]. With regard to neurological sequelae, our results were similar to those of Lagunju et al. who found the following sequelae: motor disability (83.3%), dysphasia (73.9%), learning disability (52.2%) and epilepsy (30.4%) [16].

CONCLUSION

In our context, neurological complications of sickle cell disease frequently occur around the age of 7. They are mainly cerebrovascular and infectious. Reinforcing preventive measures such as neonatal screening, vaccination, antibiotic prophylaxis, regular monitoring by trans-cranial echocardiography and improved access to hydroxycarbamide would reduce the frequency of these complications.

Conflict of Interest

The authors declare no conflicts of interest.

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