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Repeated vaso-occlusive crisis, severe anemia and poor follow-up are the main risk factors for stroke in sickle cell disease, in female children under 10 years: a retrospective cohort study in Yaounde (Cameroon)

Abstract

Introduction: the risk of stroke before the age of 18 is 11% in children living with sickle cell disease, in the absence of detection and prevention. The aim of the study was to determine the factors associated with the development of stroke in a context where transcranial Doppler ultrasound is not always available.

Methodology: This was a retrospective cohort study over a seven-year period from January 1, 2018 to December 31, 2024. The children living with sickle cell disease included in the study were organized into two groups; a group of those who had suffered a stroke and the other those hospitalized for other complications. Sociodemographic characteristics and clinical variables were analysed in order to identify factors associated with stroke using multivariate tests.

Results: Of the 1,984 cases recorded, 59 had suffered from stroke, representing an incidence of 2.9%. The factors associated with the occurrence of stroke were: age under 10 years (OR: 2.5; p=0.006), female gender (OR: 1.7; p=0.04), irregular follow-up (OR: 2.2, p= 0.001), a history of regular vaso-occlusive crises (OR: 1.8; p= 0.025), a history of severe anemia (OR: 328.5; p<0.001) or previous transient ischemic attack (TIA) (OR: 108.8; p<0.001).

Conclusion: Enhanced therapeutic monitoring of children with sickle cell disease in urban areas of Cameroon could reduce the risk of stroke, particularly in those under the age of 10 with a history of recurrent vaso-occlusive crisis and severe anemia.

Keywords: risk factor, stroke, sickle cell disease, transcranial doppler ultrasound, children, Yaoundé-Cameroon

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Introduction

Sickle cell disease is the leading genetic disorder in sub-Saharan Africa, accounting for approximately 75% of the 300,000 births worldwide each year.[1,2] In Cameroon, more than 7,000 children are born with sickle cell trait each year.[3] Sickle cell disease is the leading cause of stroke in children in Cameroon.[4,5] Stroke is the main neurological complication of sickle cell disease.[6,7] Factors that may have an impact on the brain include anemia, hyperviscosity, chronic inflammation and vascular insufficiency.[8] Stroke and silent cerebral infarction are preventable causes of morbidity and mortality in children living with sickle cell disease.[9] The pathogenesis of intracerebral infarction in sickle cell disease involves several mechanisms which include; circulatory insufficiency, intra-arterial embolization and vaso-occlusion.[10] In the absence of prevention and early detection, the risk of stroke before the age of 18 is 11%.[11]

Transcranial Doppler ultrasound can be used to screen children at risk of stroke for whom a transfusion program would reduce the risk to less than 2%.[12] However, this exam is not routinely performed in our setting, where follow-up is also sub-optimal.[13] We conducted this study with the aim of determining the factors associated with stroke in children living with sickle cell disease in a resource-limited setting.

Materials and methods

This was a cohort study with prospective data collection over a seven-year period from 1 January 2018 to 31 December 2024, conducted in two referral hospitals in Yaoundé where children are hospitalized and treated for complications of sickle cell disease. These were the Mother and Child Centre of the Chantal Biya Foundation and the Yaoundé Gynaeco Obstetric and Pediatric Hospital. All children aged 5 to 16 years living with sickle cell disease followed up in these two hospitals were included in the study. They were divided into two groups: group A consisted of those who had suffered a stroke, and group B consisted of those who had not. Those with incomplete or unusable medical records were excluded. We considered stroke to be the rapid onset of clinical signs of focal or global cerebral dysfunction, with symptoms lasting 24 hours or more or resulting in death, with no other apparent cause, as defined by the World Health Organization.[14]

The variables collected included socio-demographic characteristics, medical history, in particular the age at which sickle cell disease was diagnosed, number of in-patient admissions, history of previous sickle cell complications, prophylactic treatments, transfusions, blood count abnormalities at the time of stroke, and imaging abnormalities (brain CT Scan, magnetic resonance imaging, and transcranial Doppler ultrasound).

The data collected was expressed as mean +/- standard deviation and frequency. The difference between subjects in groups A and B was assessed using the chi-square test for non-parametric data and the unpaired Student's t-test for parametric data. A p-value < 0.05 was considered statistically significant. The institutional ethics committees of the hospitals and the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé 1 approved the study.

Results

Of the 2,007 files of children living with sickle cell disease hospitalized between 1 January 2018 and 31 December 2024, 1,984 were selected, with 59 subjects having had a stroke; giving an incidence of 2.9%. The mechanism of the lesion was ischemic in 45 subjects (76.3%) and hemorrhagic in 4 (6.8%); no abnormalities were identified on CT scans in 10 (16.9%) cases, suggesting a transient ischemic attack (TIA).

Stroke affected older children more than adolescents (p = 0.006), and there was a female predominance (p = 0.04). Regardless of the group, the average age at diagnosis of sickle cell disease was 3.5 ± 2 years (Table 1). The circumstances surrounding the diagnosis of sickle cell disease were mainly vaso-occlusive crisis (24.9%) and anemia (20.5%).

Table 1 Socio-demographic characteristics and finding of sickle cell disease in subjects with or without stroke

Variables	Stroke		Total N=1984	p-value
	Yes N=59 n(%)	No N=1925 n(%)		
Age groups (years)				
[5-10]	49 (83.1)	1270 (65.9)	1319 (66.5)	**0.006**
[10-16]	10 (16.9)	655 (34.5)	665 (33.5)	
Female	35 (59.3)	882 (45.8)	917 (46.2)	**0.04**
Male	24 (40.7)	1043 (54.2)	1067 (53.8)	
Age at detection of sickle cell disease (years)				
[0-5]	340 (17.1)	1597 (82.9)	1644 (82.9)	0.508
[5-10]	12 (20.3)	328 (17.1)	340 (17.1)	
Circumstances of the detection of sickle cell disease				
Vaso-occlusive crisis	21 (35.6)	474 (24.6)	495 (24.9)	0.688
Anemic crisis	17 (28.8)	390 (20.3)	407 (20.5)	
Hand-foot syndrome	5 (8.5)	318 (16.5)	323 (16.3)	
Systematic screening	12 (20.3)	331 (17.2)	343 (17.3)	
Others	4 (6.8)	216 (11.2)	220 (11.1)	
Not specified	0 (0.0)	196 (10.2)	196 (9.9)	

The baseline hemoglobin level was below 7 g/dl in 40.5% of subjects; 44.1% had received less than five blood transfusions regardless of group. Among the reasons for previous in-patient admissions, severe anemia and stroke/TIA were significantly more common in the stroke group (Table 2).

Table 2 Medical history of subjects with sickle cell disease with or without stroke

Variables	Stroke		Total N=1984	p-value
	Yes N=59 n(%)	No N=1925 n(%)		
Baseline hemoglobin level				
<7g/dL	24 (40.7%)	779 (40.4%)	803 (40.5%)	0.136
7-10g/dL	11 (18.6%)	426 (22.1%)	437 (22%)	
>10 g/dL	03 (5.1%)	130 (6.8%)	133 (6.7%)	
Not documented	21 (35.6%)	590 (30.6%)	611 (30.8%)	
Number of blood transfusions				
<5	24 (40.7%)	779 (40.4%)	875 (44.1%)	0.05
5-10	11 (18.6%)	426 (22.1%)	363 (18.3%)	
Not specified	03 (5.1%)	130 (6.8%)	805 (40.6%)	
Reasons for previous hospitalization				
Regular vaso-occlusive crisis	44 (74.6%)	1394 (70.3%)	1438 (72.5)	0.025
Acute chest syndrome	4 (6.8)	97 (5.1)	101 (5.1)	0.549
Severe anemia	20 (33.9)	3 (0.2)	23 (1.2)	< 0.001
Stroke/transient ischemic attacks	6 (10.2)	2 (0.1)	8 (0.4)	<0.001
Infections	18 (30.5)	786 (40.8)	804 (40.5)	0.112
Hand-foot syndrome	3 (5.1)	130 (6.8)	133 (6.7)	0.614

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Table 3 shows that, follow-up was more irregular among subjects in the stroke group, particularly with poor adherence to folic acid and hydroxyurea (8.5% vs. 23.3%). Similarly, vaccinations were not up to date for the age group in the stroke group (86.5%) compared to the other (67.5%).

Table 3 Adherence to prophylactic treatment and follow-up of patients with sickle cell disease with or without stroke

Variables	Stroke		Total N=1984	p-value
	YesN=59 n (%)	No N=1925 n (%)		
No follow-up	37 (62.7%)	818 (41.2%)	781 (40.6%)	**0.001**
Regular follow-up	14 (23.7%)	669 (33.7%)	655 (34%)	
Irregular follow-up	8 (13.6%)	497 (25.1%)	489 (25.4%)	
Folic acid intake	47 (79.7%)	1677 (84.5%)	1630 (84.7%)	0.161
Compliance	9 (15.3%)	994 (50.1%)	985 (51.2%)	< 0.001
Hydroxyurea intake	12 (20.3%)	759 (38.3%)	747 (38.8%)	0.003
Hydroxyurea compliance	5 (8.5%)	468 (23.6%)	463 (23.3%)	0.04
Prophylactic antibiotics	25 (42.4%)	646 (32.6%)	621 (32.3%)	0.628
Up-to-date vaccination status	8 (13.6%)	693 (35%)	685 (35.6%)	< 0.001
Incomplete vaccination status	51 (86.4%)	1240 (67.5%)	1291 (65%)	

According to multivariate analyses, being under 10 years of age (OR=2.5; p=0.006), female (OR = 1.7; p=0.04), having had irregular follow-up (OR: 2.2, p= 0.001), a history of frequent vaso-occlusive crises (OR: 1.8; p= 0.025), or severe anemia (OR: 328.5; p<0.001) or TIA exposed to greater risk of stroke (OR: 108.8; p<0.001); (Table 4).

Table 4 Associated factors with stroke occurrence in children with sickle cell disease: multivariate analysis

Variables	Odds ratio	IC 95%	P-value
Age group [5-10]	2.5	(1.27-5.02)	0.006
Female gender	1.7	(1.02-2.92)	0.04
No follow-up	2.2	(0.81-4.48)	0.001
Vaccinations not up to date	0.3	(0.13-0.59)	<0.001
Regular vaso-occlusive crises	1.8	(1.11-3.49)	0.025
Severe anemia with a baseline hemoglobin level <7 g/dl	328.547	(93.73-1151.59)	<0.001
Stroke/transient ischemic attacks	108.849	(21.47-551.90)	<0.001
No or low intake of hydroxyurea	0.4	(0.21-0.74)	0.003
No or low intake of folic acid	0.6	(0.33-1.21)	<0.001

Discussion

This retrospective cohort study aims to evaluate the risk factors contributing to strokes in patients suffering from sickle cell disease in a resource where transcranial Doppler ultrasound is not always available. The authors noticed that children under 10 years of age, female sex, who have had recurrent vaso-occlusive crises and severe anemia with irregular follow-up where at are risk of stroke.

The risk of stroke in children living with sickle cell disease is approximately 0.5% to 1.0% per year.[15] Without prevention and early detection, the risk rises to 11% before the age of 18.[11] While blood hyper viscosity causes the peripheral manifestations of sickle cell disease, chronic inflammatory mechanisms in the large cerebral vessels may be responsible for stroke.[16] According to the Stroke Prevention Trial in Sickle Cell Anemia study, transcranial Doppler ultrasound can be used to identify children at risk, so that chronic transfusion protocols can be put in place.[17] This could reduce the risk of initial stroke episodes by 90%.[15] However, this systematic transfusion is not part of our standard practice, and access to transcranial Doppler ultrasound is very limited in Cameroon, not only because of it's geographical unavailability, lack of awareness, but above all the high cost making it not affordably to most of those in need. Alternatives to chronic transfusions, such as hydroxyurea and other pharmacological treatments, have also been shown to be effective in improving the prognosis of patients at high risk of stroke.[17] There is equally need to improve availability of the medication needed and adherence to regular monitoring of the beneficiaries. Regarding the treatment, it is not free of charge and depending on the age and weight of the child, a monthly dose of hydroxyurea costs between 5,000 and 7,000 CFA francs corresponding to 8, 85 and 12, 39 US dollars. In a context where households live on less than $2 a day, only a few families are able to purchase this treatment, which is prescribed according to local protocols as soon as the first signs of sickle cell disease appear. This study noted irregularity in follow-up, which doubled the risk of stroke. This lack of follow-up could explain the frequency of vaso-occlusive crises, which exposed patients to 1.8 times the risk. factors that may have an impact on the brain; including anemia and vascular insufficiency.[8]

Strokes were common in children with sickle cell disease under the age of 10 and more so in girls. They were associated with; poor follow-up, repeated vaso-occlusive crises, severe anemia and a history of stroke. Babeer et al reported that a history of stroke, high mean corpuscular volume and low red blood cell count were statistically significant risk factors for stroke.[9] Similarly, authors revealed that factors associated with the occurrence of stroke included an episode of acute chest syndrome in the previous two weeks, low baseline hemoglobin levels and a history of stroke.[14] We found young age to be a risk factor in the present study. Other authors described a susceptibility age of 8 to 10 years.[9,11,12] This young age highlights the importance of follow-up, which should take place as early as possible in order to avoid the severe motor sequelae responsible for disability and cognitive disorders secondary to stroke.[18,19] Neonatal screening is not yet systematic in our context, which would reduce the morbidity and mortality associated with sickle cell disease.[3,20] Early screening would have prevented the condition from being discovered at an advanced age (over 3 years) in our series, usually, following a number of acute complications, notably vaso-occlusive crises, hand-foot syndrome and anemia (24.9%, 16.3% and 20.5% respectively).

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Early screening would also have made it possible to improve the care of these children living with sickle cell disease by ensuring regular follow-up, which was not the case in the present study. In fact, follow-up was regular in 33.7% of children. We observed irregular monitoring, which doubled the risk of stroke. According to recent recommendations, there is need to increase the use of hydroxyurea, which was low in this study (20.3%), as was also the case in other studies in our context.[21] This will contribute in preventing severe anemia, which was quite common in our study, affecting 33.9% of children who had suffered a stroke and increasing the risk of stroke by 328 times. Anemia is thought to be responsible for an increase in cerebral blood flow with acceleration and disruption of flow at the carotid siphon, the terminus of the internal carotid artery and the cervical internal carotid artery folds, which would promote endothelial damage with intima-media hyperplasia leading to stenosis.[10,12,22]

The baseline hemoglobin level of the patients in this study was mainly below 7 g/dl. This finding was described in 2021, with a reported baseline hemoglobin concentration of 7 to 8 g/dl in homozygous sickle cell patients.[23]

For secondary prevention of stroke, packed red blood cell transfusions are recommended for patients with hemoglobin levels below 10 g/dl.[24] In the present study, patients received multiple transfusions; they received normal blood (Hb AA) which is known to , increase hematocrit levels and in turn linearly increases the oxygen-carrying capacity of red blood cells and exponentially increases blood viscosity.[25] In the absence of a history of or concomitant medical complications with a first stroke was a major risk factor for subsequent stroke in the event of repeated transfusions.[24]

We found that a history of stroke was associated with the occurrence of a new one, this has been found in others studies.[9,26] Authors reported a recurrence rate of 14% within 3 months on average of the initial stroke, series.[11]

Similar result was described in the present study. In the absence of secondary prevention, there could be recurrence, as was the case in 60 to 92% of cases, according to Kirkham et al.,[24] This high prevalence of stroke and it's recurrence could be explained among others, by the low rate of hydroxyurea use in the present study and the lack of transcranial Doppler ultrasound. This would have allowed the detection of children at risk of stroke for whom a transfusion program would have been recommended in order to improve cerebral rheology and oxygenation.[12] Intracranial hemorrhage may be delayed after a cerebral infarction in patients with sickle cell disease; it is thought to be a delayed consequence of vascular problems that caused a cerebral infarction during childhood,[7] which probably could have explained the absence of lesions in 10 children with clinical signs of stroke. The significant risk of stroke in children has also been demonstrated; this risk could be reduced from 10% to 1% with blood transfusions.[1]

This study had a limitation, due to it's retrospective nature, we had incomplete files rejected that could have given specific data; meanwhile it highlights the characteristics of children who have suffered from stroke and the factors that predisposed them to it. Good medical record keeping and the implementation of a universal health coverage system would help to limit the loss of follow-up. Studies focusing on strokes with scans showing no obvious abnormalities would help to elucidate other modifiable factors involved in stroke.

Conclusion

Strokes were common in children with sickle cell disease, with a predilection for female children under the age of 10. They were associated with poor follow-up, repeated vaso-occlusive crisis, severe anemia crisis and a history of stroke. In urban areas of Cameroon, enhanced therapeutic monitoring of children with sickle cell disease could reduce the risk of stroke, particularly in children at risk.

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Conflicts of interest

The authors declare that they have no conflicts of interest regarding the study.

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