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Study of Cerebral Vascular Accidents in Children with Sickle Cell from 6 Months to 15 Years of Age at the Gabriel Toure University Hospital Center

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Abstract

Sickle cell disease is a hereditary disease that remains a public health problem in Mali. Our objective was to study strokes in children with sickle cell disease aged from 6 months to 15 years in the pediatrics department of the Gabriel Toure university hospital center. This was a retrospective descriptive study from April 1, 2019 to March 31, 2021 and prospective from April 1, 2021 to April 30, 2022, *i.e.* 3 years, which took place in the Pediatrics department of the Gabriel Toure university hospital center. During this study, we identified 22 cases of stroke among 714 children with sickle cell disease. The frequency of stroke in this population is 3.08%. The age group from1 to 5 years was the most affected with 40.9%. The average age of the patients was 7 years with extremes ranging from 1 year to 15 years and a median of 5 years. The male gender was predominant with 54.5%, for a sex ratio of 1.2. Headaches were the most common neurological antecedents (63.5%). Half of the patients were diagnosed with sickle cell disease after the onset of the stroke. The installation of the deficit was progressive in 54.5% of cases. Consciousness disorders were the most frequent reason of consultation (27.2%), followed by convulsions (18.1%). The most common neurological signs were impaired consciousness and hemiparesis with 45.5% each. The stroke was ischemic in 100% of cases. There were 95.5% of SS forms and 4.5% of Sβ^0thalassemia forms. Our patients had a hemoglobin level less than 7 g/dl in 57.1% of cases and between 7 and 9 g/dl in 42.8% of cases and hyperleukocytosis (leukocytes > 10,000/mm^3) in 95.4% of cases. The Sylvian artery was the most affected (45.5%). The fatality

rate was 22.7%.

Keywords

Sickle Cell Anemia, Vessels, Brain, Children

1. Introduction

Sickle cell anemia is the most common genetic disease in the world since the sickle cell gene is found in more than 50 million people, with a higher frequency in Africa where 150,000 to 300,000 homozygous births are recorded per year [1]. In Mali, approximately 12% of the population carries the sickle cell trait and 5000 to 6000 children are born with a major sickle cell phenotype per year [2]. In a situation of hypoxia, the polymerization of this sickle hemoglobin (Hb S) is the cause of chronic hemolytic anemia and vaso-occlusive crises which can affect any part of the body. Their cerebral location is the cause of cerebrovascular accidents, which constitute a very serious complication of sickle cell anemia and which play an important role in the morbidity and mortality of the disease [3] [4]. Strokes are generally ischemic (75% of cases), especially in children. Hemorrhagic accidents are rarer in children [4]. Over the last 20 years, the development of transcranial Doppler, CT, MRI and MR angiography has enabled, on the one hand, the reliable detection of this cerebral vasculopathy and, on the other hand, the identification of patients at high risk of stroke and the establishment of preventive therapeutic care [5]. In a study carried out in Ziguinchor/Senegal, sickle cell disease was the main cause of stroke in children with 37.6% [6]. A study carried out in the pediatrics department of the Gabriel Toure university hospital center from 2005-2010 on 450 children with sickle cell disease found a frequency of 2.88% [7]. With the advent of this modern imaging we initiated this work to see the evolution of the epidemiological, clinical and therapeutic aspects of strokes in children with sickle cell disease from 6 months to 15 years old.

2. Materials and Methods

This was a retrospective descriptive study from April 1, 2019 to March 31, 2021 and prospective from April 1, 2021 to April 30, 2022 (*i.e.* 3 years) which took place in the Pediatrics department of the Gabriel Toure University Hospital Center. It concerned children with sickle cell disease aged 6 months to 15 years, followed in the functional sickle cell treatment unit. All children with sickle cell disease confirmed by hemoglobin electrophoresis, aged 6 months to 15 years, presenting a stroke confirmed by imaging and admitted to the pediatrics department of the Gabriel Toure University Hospital Center were included. Not included were cases of stroke where the diagnosis of sickle cell anemia was not confirmed by electrophoresis, strokes not documented by imaging, and patients

over 15 years old. The variables studied were quantitative and qualitative:

- Sociodemographic: age, sex, educational level and residence of parents;
- Clinical: history of vaso-occlusive crises, clinical signs (headache, mucocutaneous pallor, jaundice, sensitivity disorder, convulsion, hemiparesis, hemiplegia, aphasia, facial paralysis, state of consciousness);
- Paraclinical: biology (hemoglobin electrophoresis, CBC, platelet level, reticulocyte level), imaging (cerebral tomography, transcranial Doppler ultrasound).

Data collection was carried out using a survey form developed and validated for this purpose, completed from the hospitalization files of patients and the sickle cell disease follow-up notebook. The data collected were entered and analyzed by Microsoft Word 2016 and SPSS software version 22. The significance threshold was set at $p \leq 0.5$.

We considered:

- Minimal after-effects, those which have not changed the patient's lifestyle (transient blindness, walking disorder, paresis);
- Serious after-effects, those which are persistent or permanent with deterioration of the patient's lifestyle (aphasia, hemiplegia, epileptiform seizure).

Ethical considerations: Consent from each parent was requested for the use of their child's records. During this study, the identity and personal data of each patient recorded in the file remained confidential. Patients will not be identified in scientific publications and/or presentations related to this study. The questionnaire developed by the pediatrics team was approved by the establishment medical commission of the Gabriel Toure university hospital center.

3. Results

3.1. Frequency

From April 1, 2019 to April 30, 2022, we included 22 children who had a stroke out of 714 children with sickle cell disease followed in the pediatrics department of the Gabriel Toure university hospital center, or 3.08%.

3.2. Sociodemographic Aspects

The male gender represented 54.5%, or a sex ratio of 1.2. The age group of 1 to 5 years was the most affected with 40.9%, followed by 6 - 10 years with 36.4%. The average age of the patients was 7 years with extremes ranging from 1 year to 15 years and a median of 5 years. The mothers were not educated in 45.5% of cases, while the level of primary education represented 40.9% of cases among the fathers. Patients not living in Bamako were 41%.

3.3. Clinical and Paraclinical Aspects

Patients had a history of headache in 63.5% before the occurrence of clinical stroke. Stroke was the circumstance of discovery of sickle cell anemia in 50% of cases. Disturbance of consciousness was the reason for consultation in six cases (27%), followed by convulsions in 18% of cases (Table 1). The clinical signs (on

admission) are dominated by loss of consciousness and hemiparesis with 45.5% each, followed by sensitivity disorders with 32% (Table 2). Pneumonitis was associated in three patients or 14% of cases.

We noted 95.5% SS form and 4.5% Sβ^0thalassemia form. The hemoglobin level was less than 7 g/dl in 59% of cases with an average level of 6.7 g/dl ± 1.7. Hyperleukocytosis was present in 21 patients or 95.4% with an average rate of 20,063 white blood cells/mm^3 ± 9.8.103/mm^3 (Table 3). Transcranial Doppler ultrasound was performed in five patients before the occurrence of the stroke, two of whom were pathological. All our patients suffered from an ischemic stroke and the sylvian artery was affected in ten cases out of 22, or 45.5% (Table 4).

3.4. Support and Evolution

All our patients were transfused urgently, then a monthly transfusion program was put in place after their discharge. The rest of the treatment was based on hyperhydration (100%), hydroxycarbamide (86%), Physiotherapy (73%), oxygen therapy (45.5%). Patients stayed in hospital between 21 and 30 days in 36% of cases. The lethality was 22.7%. The survivors presented serious after-effects in 22.5% of cases and mild after-effects in 45.4% of cases. Hemiparesis was present as a sequela in 45.4% of cases at the time of hospital discharge (Figure 1). There

Table 1. Distribution of patients according to reason for consultation.

Patterns	Frequency (n = 22)	Percentage (%)
Disturbance of consciousness	6	27
Convulsion	4	18
Headache	3	14
Axial hypotonia	3	14
Hemiplegia	3	14
Hemiparesis	2	9
Gait disorder	2	9
Others*	4	18

Others*: ptosis (1), hallucination (1) agitation (1), strabismus (1).

Table 2. Distribution of patients according to clinical signs.

Clinical signs	Frequency (n = 22)	Percentage (%)
Loss of consciousness	10	45.45
Hemiparesis	10	45.45
Hemiparesis	05	23
Sensitivity disorder	07	32
Axial Hypotonia	05	23
Facial paralysis	05	23
Aphasia	02	9
Decreased visual acuity	01	4.5
Hustle	01	4.5

Table 3. Distribution of patients according to blood count.

Hemoglobin level	Frequency	Percentage (%)
<7 g/dl	13	59
7 - 9 g/dl	9	41
Total	22	100
Leukocytes	Frequency	Percentage (%)
5000 - 9000/mm^3	1	4.6
≥10,000/mm^3	21	95.4
Total	22	100
Platelets	Frequency	Percentage (%)
150 - 499 × 10^3/mm^3	20	90.9
≥500 × 10^3/mm^3	2	9.1
Total	22	100

Table 4. Distribution of patients according to the affected vascular territory (on CT scan).

Vascular territory	Frequency (n = 22)	Percentage (%)
Cervical internal carotid artery	1	4.5
Anterior Cerebral Artery	6	27.27
Sylvian Artery	10	45.5
Posterior Cerebral Artery	1	4.5
Choroidal Artery	1	4.5
Sylvian and anterior cerebral artery	2	9.23
Sylvian and posterior cerebral artery	1	4.5
Total	22	100

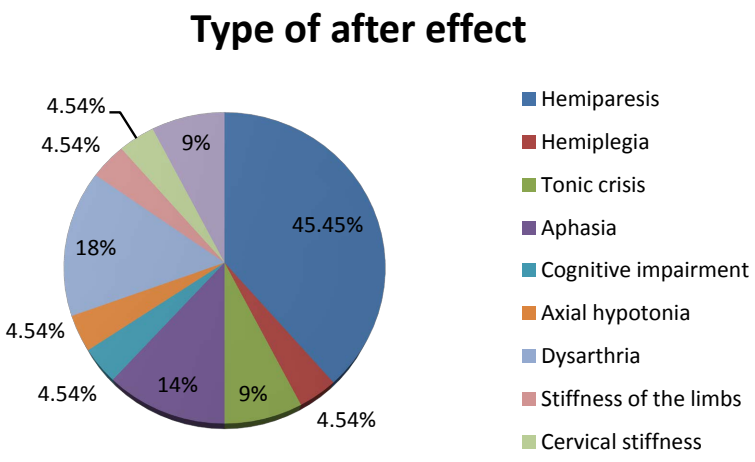

Figure 1. Distribution of patients according to the type of after-effect at discharge.

were 9% who experienced no after-effects. The patients were followed monthly to assess their progress and adapt their care.

4. Comments and Discussions

Limitations of the study:

Our study had limitations that did not prevent its completion. These included, among other things, the unavailability of magnetic resonance imaging, ideal for diagnosis; half of the patients were diagnosed following the stroke so the history is not mentioned, the frequency of attacks does not emerge.

4.1. Frequency

During our study, we recorded 22 cases of stroke in 714 children with sickle cell disease, including nine retrospective cases and 13 prospective cases. The frequency of stroke in this population is 3.08%. This result is similar to that of Ouattara A [7] who found a frequency of 2.8% in 2010.

4.2. Sociodemographic Aspects

During this study, stroke occurred in both sexes, however the male sex was predominant with 54.5%, *i.e.* a sex ratio of 1.2. This result is close to that of Rakotoharimanana V C [8], who found a sex ratio of 1.6. According to DeBaun MR *et al.* [9] male gender is a risk factor for microvasculopathy. The age group of 1 to 5 years was the most affected with 40.9% followed by 6 - 10 years with 36.4%. The average age of the patients was 7 years with extremes ranging from 1 year to 15 years and a median of 5 years. The predominance of this age group could be explained by the increase in blood circulatory speeds in the cerebral arteries in children between 3 and 12 years old with a peak around 7 - 8 years old. This result is similar to that of a study carried out in Senegal by Lemine SOM *et al.* [10] which found an average age of 7 years with extremes ranging from 10 months to 18 years. However, Coulibaly F Y found more pathological transcranial Dopplers in the age group of 1 - 10 years but with a high frequency between 6 - 10 years [11]. Patients living outside Bamako represented 41%, these are patients far from structures specializing in the management of sickle cell disease, thus delaying the diagnosis, management, and prevention of complications of the disease.

4.3. Clinical and Paraclinical Aspects

Half of the patients (eleven) were diagnosed with sickle cell disease after the occurrence of the stroke, for the other half, five were regular in follow-up and six were irregular. Which means that any delay in the diagnosis and management of sickle cell disease is a factor leading to severe complications. Ouattara A [7], found that 61.5% of patients were undiagnosed before the stroke. Headaches were the most common neurological antecedents (63.5%). They can be isolated or associated with other neurological signs such as behavioral disorder, paresis or convulsion. They can be the presumptive sign of transient ischemia which can lead to a complete infarction. Thus, any neurological sign, even a change in behavior in a sickle cell patient, should lead to a search for a stroke [12]. Disturbance of consciousness was the most frequent reason for consultation (27.3%),

followed by convulsions (18.2%). Ouattara A [7] found a predominance of convulsions (46.2%), followed by hemiplegia (23.1%). The appearance of the convulsive seizures varied: tonic seizures, atonic seizures, myoclonic seizures or even tonic-clonic seizures. Their appearance can be explained in particular by cerebral anoxia, anemia, hyperthermia and infections. The mode of installation of the deficit was gradual in 54.5% of cases and abrupt in 45.4%. Pallor was the most common clinical sign (73.2%), which is due to the chronic anemia that accompanies this disease. The most common neurological signs were disturbance of consciousness and hemiparesis with 45.4% each, followed by disturbances of sensitivity in 31.8% of cases. This result is different from that of Rakotoharimanana V C [8] who found a predominance of hemiplegia in 79% of cases, followed by dysarthria in 63% of cases. According to Bernaudin F *et al.* [13], the clinical signs most frequently presented by sickle cell patients during stroke are hemiparesis, aphasia or dysphasia with or without convulsions [13]. We noted 95.5% of SS form and 4.5% of Sβ^0thalassemia form, this could be explained by the high number of SS compared to others in the general population. Driscoll MC *et al.* in 2003, in a study which included 3425 patients, found that the frequency of strokes was 7.1% in patients with SS hemoglobin, 1.1% in patients with Sβ^0thalassemia hemoglobin, 0.6% for S/β^+thalassemia and no cases in patients with SC hemoglobin [14]. However, Coulibaly FY [11] found a higher frequency of pathological Doppler in SS than in Sβ^0thalassemia and normal velocities in SC. Our patients had a hemoglobin level < 7 g/dl in 57.1% of cases and between 7 and 9 g/dl in 42.8% of cases, with an average level of 6.7 g/dl ± 1.7. This drop in hemoglobin level leads to an increase in cerebral blood flow with acceleration and disruption of the flow at the level of the carotid siphon, the end of the internal carotid artery and the flexions of the cervical internal carotid artery, which favors damage. endothelial with hyperplasia of the intima and media therefore leading to stenosis [15]. It has also been shown that a sudden and significant drop in hemoglobin level would cause an infarction linked to tissue hypoxia by a significant drop in local cerebral blood flow [16]. The vast majority of our patients (95.4%) had hyperleukocytosis (leukocytes > 10,000/mm^3) with an average rate of 20,063/mm^3 ± 9,800/mm^3. This hyperleukocytosis has been very often described in sickle cell patients, and the high number of polynuclear neutrophils is a pejorative element in the severity of sickle cell disease. Their presence in the post-capillary venules strongly suggests (because of their volume), their major participation in the circulatory slowdown initiating vaso-occlusion. It has also been shown that sickle cell red blood cells are capable of interacting with leukocytes and particularly neutrophils [17]. All our patients (100%) had an ischemic stroke. This predominance of ischemic lesions was also found by OUATTARA A [7] and RAKOTOHARIMANANA [8] with 90.9% and 87.5% respectively. In our study, the Sylvian artery (right and left) was the most affected (45.5%). In our study, the Sylvian artery (right and left) was the most affected (45.5%). This result is similar to that of BASSE AM et col which found involvement of the sylvian artery in 49 cases out of 64 ischemic strokes (76.5%) [18]. However, ac-

cording to the literature, stroke in children with sickle cell disease is linked to progressive stenosis of the large vessels, particularly the carotid system and the middle and anterior cerebral arteries in their proximal segment [16]. The majority of our patients (77.2%) did not have transcranial Doppler ultrasound before the occurrence of the stroke due to lack of follow-up, whereas for the prevention of stroke, transcranial Doppler ultrasound must be carried out systematically once a year in all sickle cell patients from the age of two. Among the five patients who performed transcranial duplex ultrasound, two were pathological and three normal. According to Françoise Bernaudin, 20% of children with sickle cell disease will have ischemic lesions without pathological transcranial Doppler ultrasound [15].

4.4. Support and Evolution

All our patients were able to be urgently transfused with packed red blood cells. Then a transfusion program with phenotyped blood was started. This program consisted of a simple transfusion and/or transfusion exchanges with monitoring of the hemoglobin level through blood count, hemoglobin electrophoresis, and serum ferritin with the aim of lowering and maintaining the hemoglobin level S around 30%. All patients who benefited from the transfusion program showed good progress. This is similar to the result of the STOP I study, in fact, in this multicenter study (STOP I) randomizing a monthly transfusion program versus simple observation in 130 children with sickle cell disease having a pathological transcranial ultrasound with a speed greater than 200 cm/s showed that the transfusion program aimed at maintaining the HbS level below 30% made it possible to reduce the risk of stroke very significantly by 92% ($p < 0.001$) [13]. After 24 months of observation, ten strokes and one intracerebral hematoma occurred in the 67 non-transfused patients compared to a single stroke in the 63 transfused [13]. The majority of our patients (86%) benefited from treatment with hydroxycarbamide, even if no study has shown its effectiveness during stroke in sickle cell patients. It is mainly used to reduce recurrences of vaso-occlusive crises but in certain studies such as that carried out in Tunisia, it was indicated for the prevention of relapse of a cerebrovascular accident in two patients [19]. According to Bernaudin *et al.*, in the event of normalization of speeds (<170 cm/s) and in the absence of stenosis at the ARM, exit from the transfusion program with bridging by treatment with hydroxycarbamide can be proposed, subject to good compliance and after an overlap period of at least 3 months [20]. In our study, 68% of patients benefited from functional rehabilitation and we noted good neurological recovery in all these patients. Rehabilitation began as soon as the patients were stabilized. According to Bonan L *et al.*, the objective of rehabilitation is to stimulate the process of cerebral plasticity to maintain or restore altered functions and to prevent the occurrence of complications and to lead the patient to optimal autonomy regardless of the severity of the after-effects [21]. In our study, the case fatality rate was 22.7%. Among the living patients, 22.7% developed serious after-effects, 45.4% developed minimal

after-effects and 9.1% completely recovered. This fatality rate could be explained by the delay in diagnosis and treatment linked to the time (consultation) between the start of symptoms and admission to hospital and also by the severity of the brain lesion.

5. Conclusion

Stroke is a major acute complication of sickle cell disease, any neurological sign or unusual behavior should be considered. Its evolution can be punctuated by disabling after-effects or even the death of the patient. Annual screening for cerebral vasculopathy using transcranial Doppler ultrasound, emergency transfusion in any case of stroke in sickle cell patients and secondary prevention through a transfusion program can reduce the morbidity and mortality linked to this complication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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