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Stroke and Sickle Cell Disease in Children

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Abstract

Introduction: Stroke is a serious vaso-occlusive complication in children with major sickle cell syndromes. In Senegal, this topic has been little studied. Few studies have been reported about stroke in children with sickle cell disease. In order to contribute to a better knowledge of this topic, we performed this study. Our aim was to describe the epidemiological, clinical, paraclinical and evolutionary aspects of stroke, in children followed in a specialized children sickle cell unit. **Patients and Methods:** We conducted a retrospective, descriptive, and analytical study of patients treated at the Outpatient Care Unit for Children and Adolescents with Sickle Cell Disease (USAD) of the Albert Royer National Children's Hospital (CHNEAR) from May 2018 to April 2019. We included all sickle cell patients with at least one stroke. **Results:** The hospital prevalence was 2.5% and the sex ratio was 0.88. The 5 - 14 age group was the most represented. Homozygous SS sickle cell patients were the most affected (96%). Motor deficit was the main circumstance of stroke discovery (91.7%). The mean baseline Hb level was 7.7 ± 1.1 g/dl, the white blood cell level was 14538.6 ± 3816.5/mm^3, and the platelet level was 476107.1 ± 127508.8/mm^3. A brain CT scan was performed in 48 patients (75%) and a brain MRI in 5 patients (10.4%). Middle cerebral artery involvement was the most common (64.6%). A blood transfusion was performed in 56.3% of patients after the stroke. The outcome showed complete recovery of motor deficit in 10 patients (20.8%). However, recurrence occurred in 13/48 (27.1%). The main factors associated with stroke were tonsillar hypertrophy (37.5%) and adenoid hypertrophy (8.3%). **Conclusion:** Stroke was relatively common in our study. The middle cerebral artery was the most commonly affected. High obstructions were the main risk factors.

Keywords

Stroke, Sickle Cell Disease, Childhood

1. Introduction

Sickle cell disease is defined by the presence of abnormal hemoglobin S (HbS), which is capable of polymerizing in deoxygenated conditions, leading to sickling of red blood cells [1]. It is the most common genetic disease in the world, with approximately 120 million people affected. According to the World Health Organization (WHO), of the 300,000 new annual births of homozygous SS forms worldwide, more than 200,000 are in Africa, where the prevalence is estimated at 13% [2]. In Senegal, the gene prevalence is 10%, with a 0.5% risk of annual births of the major forms [3]. It is a major public health problem, due to the complications including strokes which are serious vaso-occlusive accidents. In children, stroke may induce a risk of disability, such as motor deficit, sensitive and cognitive disorders, psychological impact, but also risk of recurrence or mortality [4]. In children, stroke is an important cause of neurological morbidity and induces enormous indirect societal costs and a high burden of years with disability [5]. Most survivors have permanent neurological deficits that affect the remainder of their life [6]. Few studies have been reported on stroke in children with sickle cell disease, but not enough in our cohort. That's why we carried out this study.

Our objective was to describe the epidemiological, clinical, paraclinical and evolving profile of these strokes, in children followed in a specialized unit.

2. Patients and Methods

We conducted a retrospective, descriptive and analytical study at the Albert Royer National Children's Hospital (CHNEAR) from May 2, 2018, to April 30, 2019. We included all patients with major sickle cell syndromes who had experienced at least one stroke and were regularly monitored at the Outpatient Unit for Children and Adolescents with Sickle Cell Disease (USAD). Sociodemographic, clinical, paraclinical, and outcome data were collected using a survey form. These included stroke frequency, children's age and sex, type of sickle cell disease, comorbidities or associated factors, neurological signs, abnormalities observed on laboratory tests and imaging, as well as outcomes with sequelae. Analysis was performed using Excel 2013 and SPSS version 23.

3. Results

Among 2526 patients with major sickle cell syndromes, 64 suffered from a stroke, representing a hospital prevalence of 2.5%. The sex ratio was 0.88. The mean age at the time of the study was 149.8 ± 55.6 months (12 years 5 months), with a range of 18 months to 300 months (1 year 6 months to 25 years). Patients aged 60 to 168 months (5 to 14 years) were the majority. However, at the first stroke episode, the mean age was 76.8 ± 40.4 months (6 years 4 months), and the median was 70 months, with a range of 9 months to 182 months (9 months to 15 years). The peak incidence was at ages 60 months and older. The majority of patients, 61/64 (95.3%), were of school age, and 21 (34.4%) were in elementary school. Nevertheless, 48 patients (75%) had stroke confirmed by brain CT scan, and among them,

96% were homozygous SS (46/48). The main circumstances of stroke discovery were motor deficit (44/48, or 91.7%), seizures (10/48, or 20.8%), and language disorders (6/48, or 12.5%). This motor deficit was observed on physical examination in 33/48 patients (68.76%), mainly hemiplegia in half of the cases (50%), 24/48 patients (Table 1).

Table 1. Type and frequency of neurological signs observed in patients.

Motor deficit	Number (N = 48)	Percentage (%)
Hemiplegia	24	50
Monoplegia	5	10.4
Quadriplegia	3	6.25
Paraplegia	1	2.08
Total	33	68.76

Table 2. Neurological sequelae observed in patients.

		Number (N = 48)	Percentage (%)
Memory disorders		8	16.7
Epilepsy		14	29.2
Motor deficit	Hemiplegia	3.0	6.3
	Paraplegia	1	2.1
	Quadriplegia	3	6.3
	Total	7	14.7
Concentration disorders		4	8.3
Praxis disorders		1.0	2.1
Sphincter disorders		2.0	4.2
Superficial sensitivity disorders		1.0	2.1

Other acute complications of sickle cell disease (SCD) reported in patients were acute splenic sequestration (10.9%) and acute chest syndrome (10.9%). The patients' mean baseline Hb level was 7.7 ± 1.1 g/dl. The mean white blood cell count was 14538.6 ± 3817/mm^3 and the mean platelet count was 4761.07 ± 1275.09/mm^3. A brain computed tomography (CT) scan confirmed stroke in 48 patients. An electroencephalogram (EEG) was performed in 18/48 (37.5%), a transcranial Doppler scan in 5/48 (10.4%), and a magnetic resonance imaging (MRI) in 5/48 (10.4%). Regarding cerebral arterial abnormalities topography, the middle cerebral artery involvement was the most common, observed in 31/48 patients (64.6%) followed by anterior cerebral artery 23.3%. A blood transfusion was performed in

27/48 patients (56.2%), and hydroxyurea was prescribed in 17/48 patients (35.4%). A recurrent stroke occurred in 13/48 (27.1%) and neurological sequelae in 22/48 patients (45.8%). Among the sequelae, epilepsy was the most common, found in 14/48 patients (29.2%). Memory disorders affected 8/48 patients (16.7%), resulting in school discontinuation in 4 patients, while 36 were in special education (Table 2).

In patients, the main comorbidities were upper respiratory obstructions such as tonsil hypertrophy (18/48, or 37.5%) and adenoid hypertrophy (AH) in 4/48 patients, or 8.33%.

4. Discussion

In sickle cell disease, repeated vaso-occlusive phenomena lead to rheological disturbances, with vascular obstructions and cellular damage. The consequence is the development of proximal vasculopathy, with progressive stenosis of the large arteries or distal vasculopathy in the microcirculation. If this proximal vasculopathy is not treated, it progresses to a full-blown stroke, with a significant risk of recurrence and disabling sequelae. Previous collaborative studies in pediatrics and pediatric neurology have focused on strokes in children in general, but also on the specificities of ischemic and hemorrhagic forms in children [7]-[9]. Indeed, the epidemiology of strokes in children is poorly understood because it has been understudied. The annual incidence was estimated at 2.1/100,000 children per year in Hong Kong SAR between 1998 and 2001, with 4.5 new cases per year in children under 15 years of age. In France, this incidence was 13 cases per 100,000 children per year, while in North America, it was between 2.5 and 2.7 per 100,000 children per year. According to the Cooperative Study of Sickle Cell Disease (CSSCD), the prevalence of stroke is 3.75% [10]. In Saudi Arabia, the prevalence of stroke in SCD patients was reported to be around 4% [11]. Elsewhere, ischemic forms represented 72% and hemorrhagic forms 28% [12] [13]. In our study, the prevalence of strokes was 2.5%, a significant increase compared to previous years. Indeed, in 2015, stroke accounted for 0.75% (2 cases) of sickle cell emergencies in the same cohort [14].

In another 2015 study, stroke accounted for 45.1% of neurological manifestations in this same cohort of children [15]. This increase in stroke cases could be explained by the increase in the size of the cohort, on the one hand, and a better understanding of sickle cell disease and its complications, on the other. Indeed, the Outpatient Care Unit for Children and Adolescents with Sickle Cell Disease contributes to improving the diagnosis and management of sickle cell disease among caregivers and families through the activities of inclusion of new cases, follow-up consultation, emergency management, day hospitalization, laboratory analysis, staff training and therapeutic education. Thus, practitioners, patients and parents are trained to better understand the signs of the disease, its complications and its management. The development of pediatric neurology activity in hospitals also contributes to improving the diagnosis of these strokes. In France, in 2008, in a series

of 3,425 patients, Chekoury *et al.* reported a stroke prevalence of 7.1% in homozygous SS patients, and 11% in carriers of Sβ thalassemia. However, no cases of stroke were reported in compound heterozygotes SC [16]. In our study, we reported one case of SC and one case of Sβ thalassemia. The mean age of onset of the first stroke episode was 6 years 4 months, comparable to data in literature where the mean age ranged between 4 and 13 years [7] [17] [18]. However, the age group of 5 to 14 years was the most affected, with 62% of patients. The female predominance observed in our study was rarely reported in the literature [18]. A male predominance was described by several authors [17] [19]. Indeed, this difference could also be related to the demographic data of each country, because neither the transmission of sickle cell disease nor the occurrence of stroke is linked to sex. Clinically, the most common manifestations were motor deficits (68.76%). Hemiplegia was observed in half of the patients. In 2018, Ndiaye *et al.* also reported a clear predominance of hemiplegia (84%), followed by aphasia in 19% and focal seizures in 10% [7]. In 2021, Mbaye *et al.* found similar results, with hemiplegia in 76.3% of patients [17]. A brain computed tomography (CT) scan was performed on 48 patients.

Indeed, in our practice conditions, this is the most accessible imaging examination. It is requested as a first-line procedure and most often allows the diagnosis of stroke to be made and other causes of neurological deficits to be eliminated, such as a post-traumatic subdural hematoma, an abscess or a tumor. As a reminder, the ischemic lesion will only be seen on the CT scan 2 to 3 hours after the accident. That's why the best exam is Cerebral Magnetic Resonance Imaging (MRI). It was performed only in 5 patients (10.4%), because of its high cost and low availability for children in our country. Actually, the use of magnetic resonance angiography (MRA) is better to refine the identification of children with sickle cell disease (SCD) with a proven risk of stroke [20]. In our study, the Middle Cerebral Artery (MCA) was the most affected (64.6%), followed by the Anterior Cerebral Artery (ACA) (23.3%), the Posterior Cerebral Artery (PCA) (10.4%), and other areas (6.3%). These results were similar to data from the literature, with a clear predominance of Middle Cerebral Artery involvement [7] [8] [13] [17]. In 2024, Linguet *et al.* described few strokes without chronic stenosis and occlusion [21]. In our study, the management was primarily symptomatic. A blood transfusion was performed in 27 patients (56.3%) after the onset of the stroke, due to the unavailability of partial exchange transfusion at the time of the study. Indeed, transfusion therapies (blood transfusion and partial exchange transfusion) are the main means of stroke management in this area, in addition to general measures. Their efficacy was proven in the "STOP1" therapeutic trial. This was a study that randomized 130 patients meeting the

criterion of accelerated speed (≥200 m/s), without a history of Cerebral Arterial Infarction (CAI) into two groups; a "Transfusion" group and a "Standard Care, without transfusion" group. The results were better in the "Transfusion" group [22].

Indeed, the application of this strategy has confirmed the reduction of the risk of Cerebral Arterial Infarction in several cohorts of screened children [23] [24].

Furthermore, the establishment of a monthly partial exchange transfusion program or the use of hydroxyurea can reduce the risk of stroke recurrence [25]. During the follow-up, 10 patients (20.8%) had completely recovered from their motor deficit. According to Bernaudin *et al.* in France (2008), most patients (62.5%) had completely recovered in motor terms [26]. In Nigeria, in a retrospective study of 39 homozygous sickle cell children who had a stroke between 1998 and 2002, only 15% had completely recovered [27]. The much higher motor recovery rate in our sample could be explained by better care, thanks to the availability of a functional pediatric neurology service, early motor rehabilitation and better parental involvement, thanks to therapeutic education. However, a recurrence occurred in 13 patients, or 27.1%. This risk of recurrence is classic in sickle cell disease and exposes to neurological sequelae. Given the high recurrence rate of stroke in these patients, secondary prevention and curative measures will also be reviewed [10]. Hence the interest of secondary prevention, by transfusion therapies or by hydroxyurea. However, transfusion therapy has been shown to provide primary stroke prevention for children who have elevated cerebral artery velocity [28]. That's why transcranial Doppler (TCD) ultrasonography is useful for identifying stroke risk in children with sickle cell anemia. and recommended for stroke prevention. It allows stroke incidence to be reduced from 11% to 1% [29]. In the United States, primary stroke prevention in children with sickle cell anemia (SCA) is the standard of care with annual transcranial Doppler ultrasound to detect elevated velocities. And start initial monthly blood transfusion therapy for at least a year, followed by the option of hydroxyurea therapy. In African countries, it is not easy to have a strategy for primary stroke prevention because regular blood transfusion therapy is very difficult [30]. Previous studies have reported mixed findings on neurocognitive outcomes in children with elevated TCD [31].

In our study, the main comorbidities were upper airway obstruction. Tonsillar hypertrophy was observed in 37.5% of patients and adenoidal hypertrophy in 8.3%. Indeed, these upper obstructions induce respiratory discomfort, with a risk of sleep apnea syndrome, growth retardation, and stroke, with a risk of recurrence. The main mechanism of stroke in this area with upper obstruction is a reduction in airflow entering the airways [32]. Moreover, in 2018, in France, Corvest *et al.* found that chronic obstruction of the upper airways or the bronchial tree was a factor promoting accelerated circulation velocities in the cerebral arteries [33]. In Saudi Arabia, patients who had obstructive sleep apnea (OSA) had a higher prevalence of stroke compared to non-OSA patients by 16% with almost three times higher odds [11].

5. Conclusion

Stroke was relatively common in our study. The middle cerebral artery was the most affected. The associated factors were mainly upper respiratory obstruction.

Primary prevention should be done by transcranial Doppler to avoid its occurrence and the risk of sequelae.

Conflicts of Interest

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

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