CONTRIBUTING FACTORS TO THE OCCURRENCE OF STROKE IN SICKLE CELL HOMOZYGOUS PATIENTS

Abstract

Introduction: Stroke is a major complication of sickle cell disease, with a high morbidity and mortality rate. This study aimed to determine the contributing factors to the occurrence of stroke in homozygous sickle cell disease patients.**Patients andMethods:**We conducted a case-control study among 66 homozygous sickle cell patients, including 22 with and 44 without stroke. Stroke was diagnosed based on imaging (CT and/or MRI). Socio-demographic, clinicobiological, and evolutionary aspects were recorded for each patient.**Results:**The median age was 23 years (18 - 37) with a sex ratio (M/F) was 1.45. The most common age group was between 15 and 20 years (41.25%). The main diagnostic circumstances were persistent headache (54.5%) and hemiplegia (50%). The majority of patients had suffered an ischaemic stroke (77.3%), with a predominance of sylvian location (79.15%). Contributing factors were severalVOCs/year >3, high hemoglobin S, low baseline hemoglobin, hyperleukocytosis, high hematocrit, thrombocytosis, high LDH, and high unconjugated bilirubin.**Conclusion:**Stroke is a frightening and common complication of sickle cell disease, the occurrence of which is favored by the clinical severity of sickle cell disease and biological complications. Preventing these factors would reduce the risk of stroke in these patients.

Keywords: Sickle cell disease, Cerebral vasculopathy, Stroke, Contributing factors

INTRODUCTION

Sickle cell disease is one of the most common monogenic diseases in the world, affecting around 25 million people, including 15 million in sub-Saharan Africa. It is due to a single nucleotide substitution (GAG→GTG), affecting the sixth amino acid of the β-globin chain, leading to abnormal hemoglobin S (HbS) polymerizing in situations of hypoxia, acidosis, dehydration, and infection **[19].**Polymerization of hemoglobin S is the primum movens of the various complications of sickle cell disease, in this case, cerebral vasculopathy. Cerebral vasculopathy is the prelude to stroke, which is a major complication of sickle cell disease and is associated with a high morbidity and mortality rate**[17].**The incidence of stroke in children with sickle cell disease is 300 times higher than in a population of children without sickle cell disease **[9].**Although stenosing cerebral vasculopathy is recognized as the main cause of stroke in sickle cell disease, other clinical and/or biological risk factors may increase the likelihood of stroke. In sub-Saharan Africa, few studies have looked at the factors that contribute to stroke in adult patients with sickle cell disease. And yet, having predictive factors for the occurrence of stroke would make it possible to diagnose it early, to propose targeted treatment, and thus to have an impact on the cost of care and the quality and life expectancy of patients. This study aimed to describe the socio-demographic, clinical, and paraclinical characteristics of homozygous sickle cell patients and to identify the contributing factors to stroke.

METHODOLOGY

This was a single-center case-control study among homozygous sickle cell patients followed over 8 years (December 2012 to October 2020) who were diagnosed based onhemoglobin electrophoresis.

The study was conducted in the clinical hematology department of the Centre National de Transfusion Sanguine (Dakar, Senegal), which is the reference setting for the management of sickle cell disease in adults.

It involved 22 homozygous sickle cell patients and 44 controls consisting of homozygous sickle cell patients with no neurological pathology followed in the same department. Each case was matched with 2 controls of the same age and sex.

All patients were over 15 years of age and presented with an overt stroke during their follow-up, consisting of a sudden onset of neurological deficit associated with radiological images showing a cerebral parenchymal infarction or cerebral hemorrhage.

Patients with transient ischaemic attack (TIA) were excluded from this study.

To describe the epidemiological, diagnostic, therapeutic, and evolutionary aspects of these sickle cell patients, we studied the medical records of each patient. The diagnosis of stroke was suspected based on clinical neurological manifestations and then confirmed by imaging (computed tomography and/or magnetic resonance imaging). Additionally, a hemogram and a hemolysis assessment (LDH, haptoglobin, indirect bilirubin) were performed.Regarding the treatment, the patient systematically benefited from transfusion support (single transfusion or exchange transfusion) and symptomatic treatment. The clinical and paraclinical outcome of all recruited patients was monitored.

To identify contributing factors to the occurrence of stroke, we compared the diagnostic parameters of stroke cases with those of controls without stroke.

The data were processed using SPSS version 11.0 software. Categorical variables were presented as percentages. They were compared using the Chi2 test. Quantitative variables were presented as median (with maximum and minimum) or mean (with standard deviation). They were compared using the Student t-test; a probability of $p < 0.05$ was considered significant.

RESULTS

- **General characteristics ofpatients at baseline**
  - **Socio-demographic aspects :**

Among a population of 4,000 patients monitored for major sickle cell disease, we identified 22 patients with one or more episodes of stroke, giving a prevalence of 5.5 per 1,000. Our study population comprised 13 men and 9 women (sex ratio = 1.45); the mean age at diagnosis was 23 years (± 6.7 years).

  - **Diagnostic aspects**

The most common symptom was headache (54.6%), followed by motor deficit (50%).

Sixteen patients (72.7%) had neutrophil hyperleukocytosis; the mean leukocyte count was 15.55 G/L (±5.88 G/L). The mean hemoglobin level was 6.75 g/dl (±1.54 g/dl). All patients had thrombocytosis (mean level 626 G/L (± 154 G/L). Hemolysis assessment revealed elevated lactate dehydrogenase (LDH) levels in 81.1% of patients. Total bilirubin was elevated and predominantly unconjugated in all patients. Cerebral tomography and/or magnetic resonance imaging confirmed the diagnosis, distinguishing between ischemic (77.3%) and hemorrhagic (22.7%) forms **(Table 1).**

- **Contributing factors to the occurrence of stroke among sickle cell patients**

Clinically, only the number of VOCs > 3 per year was associated with the occurrence of stroke. Most of the factors identified were biological factors related to hemogram abnormalities (baseline hemoglobin< 8 g/dl, mean hyperleukocytosis 15.63 G/L, mean hematocrit 28.13%, mean thrombocytosis 657 G/L); hemoglobin electrophoresis abnormalities (mean HbS 94.06%) or hemolysis abnormalities (elevated LDH, predominantly unconjugated hyperbilirubinemia) **(Table 2).**

DISCUSSION

Our study aimed to investigate the contributing factors to the occurrence of stroke in patients with sickle cell disease in the clinical hematology department of the CNTS in Dakar. Most of these factors have been deduced from Western studies, despite the differences in epidemiological parameters, diagnostic and therapeutic methods, and living conditions between Africa and the West. To our knowledge, these parameters have not been studied in retrospective studies in sub-Saharan Africa, and more particularly in Senegal. Thus, given the difficulty of management and the frequency of complications and sequelae, we felt it necessary to carry out this study to identify the main contributing factors to the occurrence of stroke in homozygous sickle cell disease in our countries and to prevent it.

- **General characteristicsof patients**

In our study, the sex ratio of 1.45 showed a clear male predominance. Although this sex ratio varies from one series to another in the literature, the male predominance is almost constant **[1,6,18]**.However, a Ugandan study showed a sex ratio of 1 **[14]**.

The signs and symptoms of stroke in patients with major sickle cell syndromes are similar to those observed in patients without major sickle cell syndromes **[12]**. In our study, the most reported and most representative symptom was headache, found in 12 patients (54.6% of the population). Also in Kenya, 79.9% of patients underwent a history of recurrent headaches **[15]**. Similarly, **Hassan A. et al** reported the same results of headaches during stroke **[10]**.In addition, motor deficit was found in 50% of our patients. Similarly, in Kenya, hemiplegia and facial paralysis were present in 7/13 (53.8%) of patients; **Andrew S. et al** reported similar results **[20]**.Cerebral CT scans were performed in all our patients; cerebral ischemia was the lesion found in 17 patients (77.27%); there were 5 cases (22.72%) of cerebral hemorrhage.

This predominance of ischemic strokes could be linked to the most common age of patients, which is under 20. This result is consistent with an American

study based on a 10-year follow-up of 4,000 patients, which found that strokes were predominantly ischemic before the age of 20, with a maximum risk between 1 and 9 years, and hemorrhagic after 20 years **[5]**.Involvement of the sylvian region was found in 77.17% of our patients; similarly, **Abire Allaoui** and **Khadija Echchilali** showed in their study that the sylvian territory was affected in 80% of cases; another study carried out in Parakou showed that the territory most affected in patients with ischaemic stroke was that of the sylvian artery (73.1%) **[2]**. In a Guinean study, there were 3/6 cases of occlusive stenosis of the sylvian artery in its proximal segment **[13]**. This predominant involvement of the sylvian territory is probably explained by a greater friction force at this level. This friction is the result of a marked sinuosity of the sylvian territory associated with very high velocimetry, as supported by the Malagasy study **[11].**

[5]. [2]. [13]. [11].

- **Contributing factors to stroke in sickle cell patients**

In our study, several consultations per year of less than 3 were associated with a risk of stroke. Thus, irregular follow-up could explain the lack of detection of signs preceding stroke and, consequently, the absence of effective primary prevention. The number of VOCs greater than 3 per year was significantly found in patients who had suffered a stroke.

Biologically, our study showed that 13 patients (59.09%) had a baseline Hb level of less than or equal to 7g/dl. Eight patients had a baseline Hb level of between 7 and 9g/dl. Only one patient had a baseline Hb of 9 g/dl. Low Hb is a predisposing factor for ischaemic stroke **[10].**This means that neurological events are associated with lower Hb levels. The same result was obtained in a large prospective multicentre study in France **[23].**

Hb S levels were above 80% in all our patients. The most frequently identified risk factors for ischemic stroke in adults include genotype (risk is highest for Hb S) **[3,21]**.

The risk of stroke is highest in patients with sickle cell disease SS and sickle cell disease beta-zero thalassemia. The risk in patients with sickle cell disease SC and sickle cell disease beta plus thalassemia (particularly in young children) is significantly lower, so screening is not recommended in these patients unless there are additional concerns **[7]**.

The higher the amount of HbS in the red blood cell , the greater the falciformation. High hematocrit, an indirect reflection of blood viscosity, was a risk factor for stroke in our patients. In this respect, one study showed an increase in the internal viscosity of sickle cell red blood cells and their tendency to adhere to each other at low oxygen tension in patients with major sickle cell syndrome **[22].**The presence of sickle cells is responsible for an increase in blood viscosity and hence vaso-occlusive complications.

Loss of deformability and elasticity of the red blood cell leads to premature hemolysis**[5].**In our study, the hemolysis assessment was not normal in the majority of patients; all patients had increased total bilirubin levels; and sixteen patients had elevated LDH levels. Increased levels of hemolysis markers such as lactate dehydrogenase (LDH), bilirubin, and reticulocyte count correlate with the onset of stroke **[4,8]**. Indeed, intravascular hemolysis reduces the bioavailability of nitric oxide, leading to vasoconstriction.

CONCLUSION

This study shows that strokes in sickle cell disease are more ischemic than haemorrhagic, and occur more frequently in the sylvian region. Biological parameters impairment of the hemogram and hemolysisassessments were found to be the main contributing factors to stroke. Monitoring these parameters could reduce the risk of stroke in homozygous sickle cell patients.

CONSENT

As per international standard or university standard, parental(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Table 1: General characteristics of patients with stroke at baseline

PARAMETERS	NUMBERS	PERCENTAGES (%)
Age at stroke diagnosis (years)		
0 - 20	15	68,1
20 - 30	6	27,2
30 - 40	1	4,5
Clinical manifestations		
Headaches	12	54,50
Drowsiness	3	13,60
Convulsions	4	18,20
Languagedisorders	5	22,70
Vision disorders	2	9

Sensitivitydisorders		7	31,80
Facial palsy		3	13,60
Hemiplegia		17	77,27
Sphincter disorders		1	4,50
Territories			
Frontal		2	8,33
Left-sidedsylvian	Superficial	7	29,16
	Profound	6	25
Right-sidedsylvian	Superficial	4	16,66
	Profound	2	8,33
Multifocal involvement		3	12,5

Table 2: Main contributing factors among patients

Contributingfactors	**Patients (n=22)**		**Control (n=44)**		**P**
	Mean	**Standard deviation**	**Mean**	**Standard deviation**	
Hb F level (%)	4,28	2,31	4,86	1,47	0,243
Hb S level (%)	**94,06**	**2,93**	**88,20**	**2,83**	**0,000**
Hb level at baseline (g/dl)	**7,40**	**0,97**	**8,64**	**0,54**	**0,003**

Total Bilirubin (mg/l)	37,68	19,16	25,25	8,67	0,012
Indirect Bilirubin (mg/l)	27,09	17,37	15,95	6,81	0,012
LDH (UI/l)	**580,27**	**183,98**	**308,18**	**124,20**	**0,000**
Number of VOC/ year	**3,45**	**1,06**	**1,41**	**0,48**	**0,000**
Number of chronic complications	0,64	0,79	0,27	0,43	0,069
MCV (fl)	83,18	3,69	83,61	1,65	0,627
Hématocrite (%)	**28,13**	**2,17**	**30,18**	**1,52**	**0,001**
Number of consultations/year	**1,50**	**0,86**	**2,27**	**0,70**	**0,004**
Platelets (G/l)	**615,27**	**149,17**	**270,14**	**83,88**	**0,000**
Leukocyte (G/l)	**15,43**	**5,69**	**8,61**	**1,67**	**0,000**

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