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Original article

Factors associated with stroke in patients with sickle cell disease at the National Reference Centre for Sickle Cell Disease, Niamey, Niger, 2023

Facteurs associés aux accidents vasculaires cérébraux chez les patients drépanocytaires au Centre national de référence de la drépanocytose de Niamey, Niger, 2023

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Abstract

Introduction: Stroke is one of the most serious complications of sickle cell disease. In Niger, available data are descriptive. This study aimed to identify the factors associated with stroke in patients with sickle cell disease followed at the National Reference Centre for Sickle Cell Disease (CNRD) in Niamey.

Methods: We conducted a case-control study at the CNRD from 1 May to 15 July 2023, based on the review of follow-up records. Cases were patients with sickle cell disease (SS, Sβ, SC) who had had a stroke; each case was matched with the next two patients without stroke in the follow-up list. Factors associated with stroke were identified by multiple binary logistic regression (backward stepwise procedure).

Results: A total of 348 patients were included (116 cases and 232 controls). All cases had the homozygous SS form, and 74.1% were aged 15 years or younger. In the final model, stroke was associated with irregular follow-up (aOR = 4.00; 95% CI: 2.15–7.43) and a history of transfusion (aOR = 61.67; 95% CI: 23.38–162.61). Mothers without employment (aOR = 0.45; 95% CI: 0.23–0.89) and anaemia recorded in the follow-up file (aOR = 0.11; 95% CI: 0.03–0.35) were inversely associated with stroke. The Hosmer–Lemeshow test indicated an adequate fit (p = 0.449).

Conclusion: Irregular follow-up, transfusion history and maternal occupation were associated with stroke in patients with sickle cell disease. The apparently protective effect of anaemia should be interpreted with caution. Strengthening regular follow-up, with active recall of patients who miss appointments, is a priority.

Keywords: Stroke; sickle cell disease; associated factors; case-control study; Niger.

Résumé

Introduction : L'accident vasculaire cérébral (AVC) est l'une des complications les plus graves de la drépanocytose. Au Niger, les données disponibles sont descriptives. Cette étude avait pour objectif d'identifier les facteurs associés aux AVC chez les patients drépanocytaires suivis au Centre national de référence de la drépanocytose (CNRD) de Niamey.

Méthodes : Il s'agissait d'une étude cas-témoins menée au CNRD du 1er mai au 15 juillet 2023, à partir de la revue des dossiers de suivi. Les cas étaient des drépanocytaires (SS, Sβ, SC) victimes d'AVC ; chaque cas était associé aux deux patients sans AVC qui le suivaient dans la file active. Les facteurs associés ont été recherchés par régression logistique binaire multiple (procédure pas à pas descendante).

Résultats : Au total, 348 patients ont été inclus (116 cas et 232 témoins). Tous les cas présentaient la forme homozygote SS et 74,1 % avaient 15 ans ou moins. Dans le modèle final, l'AVC était associé au

suivi irrégulier (ORa = 4,00 ; IC 95 % : 2,15–7,43) et aux antécédents de transfusion (ORa = 61,67 ; IC 95 % : 23,38–162,61). Les mères sans emploi (ORa = 0,45 ; IC 95 % : 0,23–0,89) et l'anémie consignée dans le dossier (ORa = 0,11 ; IC 95 % : 0,03–0,35) étaient inversement associées à l'AVC. Le test de Hosmer-Lemeshow indiquait une bonne adéquation du modèle (p = 0,449).

Conclusion : Le suivi irrégulier, les antécédents de transfusion et la profession de la mère étaient associés à l'AVC chez les drépanocytaires. Le caractère apparemment protecteur de l'anémie doit être interprété avec prudence. Le renforcement d'un suivi régulier, avec un rappel actif des patients perdus de vue, est prioritaire.

Mots-clés : Accident vasculaire cérébral ; drépanocytose ; facteurs associés ; étude cas-témoins ; Niger.

Introduction

Stroke is defined as "rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" [1]. Stroke occurs most often in people with hypertension, diabetes, kidney disease or advanced age, and also in patients with sickle cell disease. Sickle cell disease, the most common genetic disease worldwide, affecting around 50 million people [2], is a leading cause of stroke in both children and adults [3]. According to the World Health Organization (WHO), stroke affects nearly 8% of children with sickle cell disease worldwide [4].

Ohene-Frempong et al. reported that the spontaneous risk of stroke increases with the age of the patient with sickle cell disease. The probability of a first stroke was estimated at 11% by the age of 20 years, 15% by 30 years and 24% by 45 years in patients with SS and $S\beta^0$ genotypes [5]. In sub-Saharan Africa, a systematic review of 10 articles from seven countries found a prevalence ranging from 2.9% in Nigeria to 16.9% in Tanzania [6]. The severity of stroke lies in the risk of disabling complications. Stroke prevention in sickle cell disease relies on early detection of stroke risk with transcranial Doppler ultrasound and the initiation of lifelong hydroxyurea treatment.

In Niger, an increase in the number of strokes among patients with sickle cell disease has been observed, hence the need to identify the associated factors that might explain this rise. The main associated factors reported in the literature are age, sex, the type of haemoglobinopathy, severe anaemia and transfusions [5, 7–13]. Most of these studies were prospective longitudinal or retro-prospective studies.

In Niger, existing data come from descriptive studies. To shed more light on the associated factors, we conducted a case-control study of clinical factors, such as the frequency of vaso-occlusive crises (which we hypothesised to be the main risk factor), and of sociodemographic factors.

The aim of our study was to identify the factors associated with stroke in patients with sickle cell disease in a hospital setting at the National Reference Centre for Sickle Cell Disease in Niamey in 2023.

Methods

The study was conducted at the National Reference Centre for Sickle Cell Disease (CNRD). The CNRD is a public scientific, technical and cultural institution under the technical supervision of the Ministry of Public Health and Hygiene (MSP/HP). Located in Niamey, it receives patients from all regions of Niger.

This was a case-control study carried out at the CNRD from 1 May to 15 July 2023.

Cases were patients with sickle cell disease (SS, Sβ, SC) who had had a stroke and who had a usable medical record with an identification number in the active follow-up list. Controls were patients with sickle cell disease (SS, Sβ, SC) from the same list who had not had a stroke, with two controls per case.

Cases were selected consecutively from the active follow-up list, starting from 2014, until the planned number was reached. Each time a case was identified, the two patients immediately following it in the list were selected as its controls.

Sample size was calculated with the STATCALC function of Epi-Info® version 7.2.5.0 using the Kelsey method, with the following parameters: 95% confidence level, 80% power, two controls per case, a frequency of vaso-occlusive crisis (VOC) of 54.9% [14] and an expected odds ratio of 2. This gave a minimum sample of 348 patients, comprising 116 cases and 232 controls.

The dependent variable was the occurrence of stroke. The main exposure of interest was the frequency of vaso-occlusive crises.

Data were collected with a questionnaire through a review of the records of the active follow-up list. Data were entered with Epi-Info® 7.2.5.0 and analysed with Stata® version 14.

A descriptive analysis with calculation of proportions was performed. Odds ratios with their

95% confidence intervals and p-values were estimated.

Simple binary logistic regression was then performed. All variables associated with stroke with a p-value ≤ 0.20 were entered into the multiple binary logistic regression model, adjusting for sociodemographic, clinical, biological and genetic characteristics. The main exposure of interest was also forced into the initial model.

A backward stepwise procedure was used for the multivariable analysis. The final model retained only independent variables with a p-value < 0.05. The goodness of fit of the final model was assessed with the Hosmer–Lemeshow test.

Administrative authorisations were obtained from the Ministry of Public Health and Hygiene, the coordination of the BFELTP programme and the CNRD. Ethically, the database was anonymised, and patient confidentiality and anonymity were respected.

Results

A total of 348 patients with sickle cell disease were selected. Overall, 74.1% of cases and 60.8% of controls were aged 15 years or younger. Among stroke cases, 52.6% were male, compared with 44.0% of controls. All stroke cases (100%) had the homozygous SS form. In addition, 31.0% of cases lived in rural areas, compared with 44.0% of controls (Table I).

Table I: Distribution of cases and controls according to sociodemographic, genetic, biological and clinical characteristics, CNRD, Niamey, 2023

Factors studied	Cases, n (%) N = 116	Controls, n (%) N = 232	p-value
Age (years)			0.014
> 15	30 (25.9)	91 (39.2)	
≤ 15	86 (74.1)	141 (60.8)	
Sex			0.129
Male	61 (52.6)	102 (44.0)	
Female	55 (47.4)	130 (56.0)	
VOC frequency			0.001
Low	100 (86.2)	223 (96.1)	
High	16 (13.8)	9 (3.9)	
Mother's education			0.004
Educated	52 (44.8)	68 (29.3)	
No formal education	64 (55.2)	164 (70.7)	
Father's education			0.349
Educated	88 (75.9)	165 (71.1)	
No formal education	28 (24.1)	67 (28.9)	
Mother's occupation			0.063
Employed	35 (30.2)	49 (21.1)	
Not employed	81 (69.8)	183 (78.9)	
Father's occupation			0.187
Employed	97 (83.6)	180 (77.6)	
Not employed	19 (16.4)	52 (22.4)	
Place of residence			0.020
Urban	80 (69.0)	130 (56.0)	
Rural	36 (31.0)	102 (44.0)	
Type of haemoglobinopathy			< 0.001
SC	0 (0.0)	39 (16.8)	
SS	116 (100)	193 (83.2)	

Factors studied	Cases, n (%) N = 116	Controls, n (%) N = 232	p-value
Follow-up visits per year			< 0.001
Regular	48 (41.4)	148 (63.8)	
Irregular	68 (58.6)	84 (36.2)	
Anaemia			0.003
No	94 (81.0)	213 (91.8)	
Yes	22 (19.0)	19 (8.2)	
ACS			< 0.001
No	106 (91.4)	230 (99.1)	
Yes	10 (8.6)	2 (0.9)	
Transfusion			< 0.001
No	40 (34.5)	207 (89.2)	
Yes	76 (65.5)	25 (10.8)	
Presence of HbF			0.413
No	33 (28.4)	76 (32.8)	
Yes	83 (71.6)	156 (67.2)	

VOC: vaso-occlusive crisis; ACS: acute chest syndrome; HbF: foetal haemoglobin.

In simple binary logistic regression, only father's education and the presence of HbF had p-values above 0.20 (Table II).

Table II: Association between the factors studied and stroke in simple binary logistic regression, CNRD, 2023

Factors studied	Cases, n (%) N = 116	Controls, n (%) N = 232	OR	95% CI	p-value
Age (years)					0.014
≤ 15	86 (74.14)	141 (60.78)	1.85	1.13–3.02	
VOC frequency					0.001
High	16 (13.79)	9 (3.88)	3.96	1.69–9.27	
Anaemia					0.003
Yes	22 (18.97)	19 (8.19)	2.62	1.35–5.07	
Sex					0.129
Male	61 (52.59)	102 (43.97)	1.41	0.90–2.21	
Mother's education					0.004
No formal education	64 (55.17)	164 (70.69)	0.51	0.32–0.81	
Father's education					0.349
No formal education	28 (24.14)	67 (28.88)	0.78	0.46–1.30	
Mother's occupation					0.063
Not employed	81 (69.83)	183 (78.88)	0.61	0.37–1.02	
Father's occupation					0.187
Not employed	19 (16.38)	52 (22.41)	0.67	0.37–1.21	
Place of residence					0.020
Rural	36 (31.03)	102 (43.97)	0.57	0.35–0.91	
Follow-up visits per year					< 0.001
Irregular	68 (58.62)	84 (36.20)	2.49	1.58–3.93	
ACS					< 0.001

Factors studied	Cases, n (%) N = 116	Controls, n (%) N = 232	OR	95% CI	p-value
Yes	10 (8.62)	2 (0.86)	10.84	2.33–50.38	
Transfusion					< 0.001
Yes	76 (65.52)	25 (10.78)	15.73	8.94–27.66	
Presence of HbF					0.413
No	33 (28.45)	76 (32.76)	0.82	0.50–1.33	

OR: odds ratio; CI: confidence interval; VOC: vaso-occlusive crisis; ACS: acute chest syndrome; HbF: foetal haemoglobin.

After adjustment, the factors associated with stroke in patients with sickle cell disease at the CNRD in Niamey in 2023 were anaemia, maternal employment, irregular follow-up and transfusion history (Table III).

Table III: Factors independently associated with stroke in the 348 patients with sickle cell disease, CNRD, Niamey, 2023

Factors studied	aOR	95% CI	p-value
Anaemia: yes	0.11	0.03–0.35	0.001
Mother: not employed	0.45	0.23–0.89	0.023
Follow-up: irregular	4.00	2.15–7.43	0.001
Transfusion: yes	61.67	23.38–162.61	0.001

aOR: adjusted odds ratio; CI: confidence interval. Hosmer–Lemeshow test: p = 0.449 (> 0.05), indicating an adequate fit of the final model.

Discussion

This study, conducted at the CNRD in Niamey in 2023, included 348 patients. The factors significantly associated with stroke were irregular follow-up, anaemia, transfusion and maternal employment.

The study showed that irregular follow-up was a predictor of stroke. This is an original finding, as this factor has not been reported in the available literature. Regular follow-up is essential in the management of sickle cell disease because it allows complications to be detected early. Stroke screening relies on transcranial Doppler ultrasound, performed annually when the result is normal and every six months when it is abnormal. Irregular follow-up therefore prevents monitoring of the vasculopathy as well as of certain biological factors that favour stroke, such as leucocytosis and thrombocytosis.

Although transcranial Doppler is the reference investigation for stroke-risk screening in children with sickle cell disease, it could not be included as a variable in our analysis. This examination was only introduced into the routine follow-up assessment in 2017, whereas our study period began in 2014, so the information was not available for all included patients. An important avenue for future research would be to assess, in a study covering the period after 2017, the direct association between the actual performance of transcranial Doppler and the occurrence of stroke.

The study also found that anaemia was inversely associated with stroke, a result that contrasts with that reported by Munube et al. in Uganda [7]. This discrepancy may be explained by limitations inherent in our data source, which was restricted to follow-up records. Some patients may have received an emergency transfusion on admission or in the three months preceding the stroke, and the corresponding blood counts, recorded in inpatient files, were not accessible for this study. This apparently protective effect of anaemia (aOR = 0.11) must therefore be interpreted with caution, all the more so because anaemia was positively associated with stroke in the crude analysis (OR = 2.62) and its direction reversed only after adjustment for transfusion history, which was very strongly associated with stroke; this pattern suggests confounding between anaemia and transfusion rather than a true protective effect. This counter-intuitive association may be explained by recent transfusions not documented in the follow-up files, which could have normalised haemoglobin levels while reducing the actual risk.

Our results also showed that patients whose mothers were employed were more frequently affected by stroke. This may be because working mothers spend less time with their children, so that therapeutic education instructions may be poorly applied. These mothers may also more often miss sickle cell follow-up appointments, which are essential for the

detection, prevention and monitoring of major complications of the disease, including stroke.

A history of transfusion was also found to be a predictor of stroke in patients with sickle cell disease: transfused patients were more exposed to stroke. This is consistent with the results of two studies conducted in Uganda and the United States [5, 7]. It may be explained by the fact that repeated transfusions, especially with whole blood, provide additional white blood cells and platelets, which contribute to thrombus formation and thus to stroke.

However, after adjustment, no independent association was found between stroke and the main exposure of interest, the frequency of vaso-occlusive crises. This may be because most patients seek care only for major crises or when a first warning sign appears, such as motor deficit or aphasia. Minor crises do not require a consultation and are managed at home.

Strengths and limitations

Like any study, this one has strengths and limitations.

Unlike the cross-sectional studies usually conducted, the case-control design allowed different associated factors to be identified. Two new factors not previously reported in the literature were thus identified: irregular follow-up and maternal employment.

The study covered a well-defined period (2014–2021), during which cases were identified and matched with two controls each. It was, however, a hospital-based study limited to patients followed at the CNRD, and not all patients who have a stroke are admitted to this facility.

The retrospective design, based on existing records, exposes the study to information bias, as some of the information collected may no longer be up to date. This bias particularly concerns minor vaso-occlusive episodes managed at home without consultation and emergency transfusions, which are inconsistently recorded in medical files. Such under-reporting may have affected the accuracy of some variables in our analysis, especially undocumented transfusions, as discussed above.

In addition, data on stroke recurrence and on patients' vital status during follow-up were not systematically available in the records reviewed, which prevented us from exploring the factors associated with recurrence or mortality.

These results call for stronger follow-up strategies for patients with sickle cell disease, both at the CNRD and nationwide. Since irregular follow-up emerged as a major predictor, particular attention should be paid to active recall through a follow-up register at the CNRD to identify patients who have missed their appointments, although its implementation depends on the availability of dedicated human and logistical resources. Strengthening therapeutic patient education, involving all those who care for the child and not only the mother, appears to be an essential lever.

Conclusion

In this study, irregular follow-up, transfusion history and maternal occupation were associated with stroke, while anaemia recorded in the follow-up file was inversely associated with it, a finding that requires cautious interpretation. All affected patients had the homozygous SS form, and most were aged 15 years or younger. These findings highlight the need for regular, strengthened follow-up to prevent this severe complication.

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