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Stroke without cerebral arteriopathy in sickle cell disease children: causes and treatment

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Running Title
Atypical stroke in sickle cell disease

Ischemic strokes in children with SCD can be related to causes other than classical cerebral arteriopathy. They affect a different population of patients and may require specific management.

Keywords: Sickle Cell Disease, Stroke, Arteriopathy

Authorship Contributions
SLL, SV and BK collected and analysed the data; FM, LHV, VB, GI, MB are in charge of the patients, revised the clinical and biological data; SV, AN and MK revised the radiological data prepared the figures; EL revised the transfusion data; SLL, MK and BK wrote the manuscript; MK and BK supervised the study. All the authors discussed the results and contributed to the final manuscript.

Disclosure of conflicts of interest
The authors declare no competing financial interests.

Sharing Statement
Data are available on request to the corresponding author.
Abstract

Cerebral arteriopathy (CA) in children with sickle cell disease (SCD) is classically described as chronic stenosis of arteries in the anterior brain circulation, leading to ischemic stroke. Some studies have however reported strokes in children with SCD but without CA. In order to better understand the etiology and risk factors of these strokes, we retrospectively analyzed ischemic strokes occurring in a large cohort of children over a 13 year-period.

Between 2007 and 2020, 25/1500 children with SCD had an ischemic stroke in our center. Among them, 13 (52%) had CA, described as anatomical arterial stenosis, while 12 (48%) did not. Patients with stroke without CA were older than patients with stroke attributed to SCD-CA (9.0 years old vs 3.6 years old, \( p=0.008 \)), and had more frequently a SC genotype (25% vs 0% respectively). Their stroke involved posterior circulation more frequently, with cerebellar involvement in 42%. Retained stroke etiologies in patients without typical SCD-related CA were reversible cerebral vasoconstriction syndrome, cerebral fat embolism, arterial thrombosis or thromboembolism, hyperviscosity, vasculitis in a context of infectious meningoencephalitis, and severe hemodynamic failure. No recurrence was observed in the 24 months following stroke, even though 67% of the patients were no longer receiving exchange transfusions in this group. In conclusion, in a cohort of pediatric SCD patients with efficient stroke screening strategy, half of occurring ischemic strokes were related to causes other than CA. They affected a different population of SCD children and systematic long-term transfusion programs may not be necessary in these cases.
Introduction

Stroke is one of the most severe complications affecting children with sickle cell disease (SCD)\(^1\), occurring in about 7.4% of children with sickle cell anemia (SCA) by the age of 14 years old in the absence of a preventive strategy\(^2\). Children with SCA between 2 and 5 years of age have the highest risk of ischemic stroke, with an incidence of 1% per year\(^3\). Overt stroke is mainly related to chronic stenosis and occlusion of large cerebral arteries in the anterior circulation resulting from intimal thickening\(^4,5\), described as cerebral arteriopathy related to SCD (SCD-CA). The internal carotid, including its extracranial part\(^6\), middle cerebral, and anterior cerebral arteries are often involved in ischemic stroke\(^7,8\) and up to 71% of SCA patients with a history of overt stroke have been reported to have large-vessel arteriopathy in the anterior circulation territories\(^9\). Without secondary prevention based on a long-term transfusion program, the recurrence rate after a first ischemic stroke is very high, reaching 67% for a mean observation time of 9 years in Powars study, with 50% of the events occurring within 2 years after the initial event\(^10\).

Screening for SCD-CA is based on routine annual transcranial Doppler sonography (TCD) for all children with SCA, starting in the second year of life. In patients with abnormally high blood flow velocity in one or more arteries, brain magnetic resonance imagery (MRI) and magnetic resonance angiography (MRA) are also performed to quantify severity and to investigate possible parenchymal injury or anatomical arterial stenosis. The primary stroke prevention strategy consists in monthly transfusion or exchange transfusion until normalization of blood flow on TCD and sometimes regression of stenosis, if any, on MRA\(^11\). This preventive strategy has shown to reduce the risk of ischemic stroke in children with SCA to less than 2% by 18 years of age\(^12\).

Although the natural history of cerebral arteriopathy in SCD is relatively well known, as is its correlation with the risk of ischemic stroke, several cases of ischemic stroke in children with SCD who did not have “typical” SCD-CA, i.e. as described above, have been reported\(^8,9,13,14\). This suggests that other pathophysiological processes may be present in SCD patients. Indeed, SCD is responsible for a hypercoagulability state\(^13\) and a higher risk of severe bacterial infections\(^15\), which can lead to neurological complications. Our study aimed to investigate the prevalence of ischemic stroke without abnormal TCD or anatomical stenosis of the intracranial or cervical arteries in a large cohort of children with SCD. The secondary objective was to provide an overview of the etiological diagnosis of these ischemic strokes and to raise questions regarding the specific therapeutic management of these patients.

Methods

Patients

The SCD Referral Center at Robert Debre Hospital (Paris, France) is in charge of an active list of 1300 children with SCD. All patients with SCA (homozygous or S\(^\beta^0\) genotype) undergo routine annual TCD from 18–24 months of age. If TCD was abnormal, cerebral MRI was performed to complete the neurological screening. In accordance with international recommendations, patients with abnormal TCD were re-evaluated in the next 3 months and, in the event of persistent abnormality or pathological Doppler (>200 cm/s), transfusion therapy was promptly initiated. Around 15% of the patients in our SCD cohort have the SC genotype and are not concerned by routine screening for cerebral vasculopathy, as recommended\(^11\).

In this study, we retrospectively analyzed data from all patients with SCD (any genotype), between 0 and 18 years of age who had a stroke between 2007 and 2020. Stroke was defined as an acute neurological deficit with a consistent recent arterial infarction on brain MRI. Patients with hemorrhagic stroke, cerebral venous thrombosis, or posterior reversible encephalopathy syndrome were excluded.

As SCD-related cerebral arteriopathy is a chronic cerebral arteriopathy involving anterior circulation, in this study only arteriopathies involving ICA (internal carotid artery), MCA (middle cerebral artery) or ACA (anterior cerebral artery) and with persisting MRA or TCD abnormality at 3 months post-stroke\(^16\) were labelled SCD-CA. Stroke was thus termed as “typical” if (i) associated with SCD-related cerebral arteriopathy (SCD-CA) and (ii) located in the cerebral territory of identified stenosis or abnormal TCD. Stroke was termed as “atypical” in patients who did not meet these criteria.

Steady-state biological data were collected at least 4 weeks before the stroke and at a distance from any clinical event or therapeutic escalation. To evaluate the context in which the stroke occurred we reviewed the results of biological tests performed in the 24 hours preceding the neurological episode, when available.
The study was approved by the local ethics advisory committee (registration number: 20200113123118) and oral information about the database and its use was provided to the patients and their legal guardians.

**Statistical Analysis**

The results of the descriptive analysis were expressed as numbers and percentages for categorical variables and as quartiles for quantitative variables. Because of the relatively small sample size, all statistical analyses were performed using non-parametric tests (Mann-Whitney). Statistical significance was set at p < 0.05 with a 95% confidence interval (CI). All statistical analysis results were generated using GraphPad Prism software (version 7.00).

**Results**

Between 2007 and 2020, 25 patients were managed for an acute ischemic stroke at our Sickle Cell Referral Center.

In about half of the patients in our study (n=13/25), stroke was considered as “typical” in the context of SCD. Although all of them were theoretically eligible for routine screening for CA, 6 of the 13 patients had not actually undergone TCD in the previous 12 months: 4 were lost to follow-up, 1 had just arrived from Africa and 1 had failed to undergo adequate cerebral blood flow measurement on TCD because of narrow temporal windows. Among the 7 patients with proper screening for CA, 6 had normal TCD in the previous 12 months, but abnormalities after stroke occurrence, showing progression of CA between the two screening examinations, and one had known abnormal TCD and was undergoing chronic exchange transfusion for stroke prevention at the time of the neurological event.

In 12 patients (48%), the classical definition of stroke related to SCD cerebral arteriopathy was not met and stroke was classified as “atypical”. In this group, in the 9/12 patients who were eligible for routine screening for CA, i.e. patients with SS and Sβ0 genotype, 7 had normal TCD and/or cerebral MRI findings in the 12 months before stroke occurrence. For the two patients without brain imaging in the previous 12 months, one had no temporal bone window and the other had missed appointments.

While the majority of patients with stroke (80%) had a homozygous genotype, SC genotype was more frequent in the group with “atypical” stroke: 25% vs 0% in the group with “typical” stroke. The main baseline characteristics of the 25 patients prior to stroke are presented in Table 1.

Considering biological parameters, we observed a lower leukocyte count and a lower fetal hemoglobin (HbF) rate in the group with “atypical” stroke compared to the group with “typical” stroke (11.3 10^9/L vs 15.8 10^9/L, p=0.04 and 6.2% vs 13.2% p=0.01, respectively), probably related to the older age and the higher proportion of children with SC genotype in the “atypical” stroke group.

**Stroke Characteristics**

Median age at stroke onset was significantly older in the group with “atypical” stroke as compared to the group with “typical” stroke, at 9.0 years of age vs 3.6 years of age (p=0.008). While clinical presentation was similar in the two groups with hemiplegia and/or language impairment, and in some patients, headaches, seizures and impaired consciousness, stroke occurred in significantly different settings. In the “atypical” stroke group, 7/12 strokes (58%) occurred during or shortly after a hospital stay in the intensive care unit (ICU) for delayed hemolytic transfusion reaction (DHTTR, n=1), severe parvovirus B19 infection with bone marrow necrosis and macrophage activation syndrome (n=1), severe acute chest syndrome (ACS, n=2), decompensated nephrotic syndrome (n=1), decompensated septic shock (n=1), or hospitalization for a procedure requiring general anesthesia (n=1). Conversely, in the “typical” stroke group, only 1 child was in the ICU at stroke onset, the reason being ACS. Notably, 3 children in the “atypical” stroke group had received IV corticosteroids during the 2 weeks preceding the stroke vs only one in the “typical” stroke group. The symptoms accompanying the event, i.e. hypoxia, acute anemia, fever, and vaso-occlusive crisis (VOC) did not differ between the two groups. Stroke characteristics are summarized in Table 2.

Laboratory assessments showed that in the “atypical” stroke group, hemoglobin (Hb) levels at the time of stroke were significantly higher than in the “typical” stroke group at 11.0 g/dL versus 7.4 g/dL (p = 0.027). Notably, 58% of the children in the “atypical” stroke group had Hb levels above 10.5 g/dL at the time of the stroke, which can lead to a risk of increased blood viscosity in patients with SCD.
Infarct Location and acute management

In accordance with the common topography of CA and ischemic strokes in children with SCD, 92% of the children in the group with “typical” stroke had ischemic lesions in the anterior cerebral circulation territory and 100% of them had, by definition, arterial stenosis in an artery upstream of the ischemic territory on 3D time-of-flight MRA, i.e. within the anterior cerebral circulation, specifically the cervical internal carotid, intracranial internal carotid, middle cerebral or anterior cerebral arteries.

In contrast, patients in the “atypical” stroke group presented ischemic lesions in the territory of the vertebro-basilar arterial circulation in 42% of cases. Cerebellar ischemic injury was observed only in the “atypical” stroke group.

In the “atypical” stroke group, arterial abnormalities on 3D time-of-flight MRA were observed in 4/12 patients. Two patients had diffuse arterial caliber abnormalities in both the anterior and posterior brain circulation (Patients 1 and 2, Table 3), one patient had major bilateral arterial thrombosis of the carotid arteries, the left middle cerebral and the left anterior cerebral arteries with a downstream ischemic lesion (Patient 3), and one patient had thrombosis of the basilar artery with a downstream ischemic lesion (Patient 4). For the remaining 8 patients in this group, no arterial abnormalities were found on MRA at the time of the stroke or 3 months after.

Acute stroke management was globally similar in the two groups. (Table 3).

Etiologies in “Atypical” Strokes

When the cerebral ischemic lesions identified on cerebral MRI after the stroke were in the territory of an artery whose blood flow continued to be abnormally high on TCD and/or when persistent stenosis was identified on cerebral MRI, the patient was considered to have “typical” stroke related to CA in SCD.

If not, various other etiological mechanisms of stroke were discussed in multidisciplinary team meetings. Overall, 6 different diagnoses were put forward for the 12 patients with “atypical” stroke (see Table 3, with a selection of relevant imaging in Figure 1).

Two patients had a diagnosis of reversible cerebral vasoconstriction syndrome (RCVS). RCVS is a clinical-radiological entity typically seen in middle aged women and is relatively rare in children, that associates acute “thunderclap” headaches with multifocal alternation of segmental narrowing and dilatation of the cerebral arteries on angiography (MRA, CTA or conventional angiography). These radiological abnormalities are reversible in 1 to 3 months. A triggering factor is often reported. One of our cases (Patient 1, Table 3) involved a 4-year-old girl with Sβ0 SCA hospitalized in the ICU for a delayed hemolytic transfusion reaction (DHTTR). Because of a very low Hb level, she received a red blood cell (RBC) transfusion and combined treatment with corticosteroids and eculizumab to limit the risk of DHTTR recurrence, increasing her Hb level from 2.7 g/dL to 9 g/dL. She experienced a stroke 6 days later. Cerebral and angiographic imaging was compatible with RVCS (Figure 1 panel A and Figure 2 panel A). The second case (Patient 2, Table 3) involved a 9-year-old girl with SC genotype whose symptoms occurred immediately after short-acting general anesthesia for digestive endoscopy. At that time, she had a higher than usual Hb level at 13 g/dL for a baseline of 10 g/dL (Table 3). High blood pressure was present at stroke onset in Patient 1 but only the day stroke onset in Patient 2.

One patient had a diagnosis of typical cerebral fat embolism (Patient 10; Table 3, Figure 1B). She was a 13-year-old girl of SC genotype, who had a stroke during hospitalization for severe primary infection with parvovirus B19 complicated by acute bone marrow necrosis.

In 5 cases, thrombosis or thromboembolism was diagnosed (Patients 3 to 7, Table 3, Figure 1 panel C and Figure 2 panel B). All 5 patients had an SS genotype. Cardiac ultrasound without contrast found no persistent foramen ovale in any of the patients and none of them had major abnormalities on thrombophilia assessment. Two of them had thrombosis within the posterior circulation leading to an ischemic lesion of the cerebellum, a few hours after physical effort (dancing) or in a context of acute respiratory distress syndrome (ARDS) following a severe ACS in the ICU. This last patient received corticosteroid therapy after two exchange transfusion sessions. He had a massive posterior stroke 72 hours after the beginning of the corticosteroid therapy and died 2 days later.

One patient had a stroke in a context of infectious meningoencephalitis due to pneumococcus with systemic inflammatory syndrome (Patient 11, Table 3, Figure 1D).

Another patient, a 5-year-old boy with SS genotype (Patient 12, Table 3) had a hemodynamic stroke related to systemic hemodynamic failure. During hospitalization for painful VOC, he had a generalized seizure during a
sudden episode of hypotension requiring volume resuscitation, after inhalation of an equimolar mixture of oxygen and nitrous oxide (EMONO) used as a painkiller. The stroke was confirmed on MRI showing ischemia of the antero-posterior watershed territories (Figure 1E). In the absence of any other etiology to explain the sudden drop in blood pressure, EMONO use was incriminated as a diagnosis of exclusion and the stroke was considered as from iatrogenic origin.

Lastly, in two cases, the main etiologic factor was blood hyperviscosity, based on a combination of clinical, laboratory and radiological features. Indeed, both patients had Hb levels > 13 g/dL and hematocrit higher than 35% at the time of the stroke. One patient, a 2-year-old boy with SS genotype, had a relapse of nephrotic syndrome treated with corticosteroid therapy and blood transfusion, with hyperleukocytosis at 48 x10^9/L 24 hours before stroke onset (Patient 9, Table 3). MRI showed ischemic-hemorrhagic lesions of the centrum semiovale. The second patient (Patient 8, Table 3), a 14-year-old girl with SC genotype, had a stroke within minutes of waking up, with aphasia and right hemiparesis. Her first blood analysis showed Hb at 13.6 g/dL, 3 grams higher than her baseline level. MRI found ischemia in the deep left MCA territory indicating involvement of perforating arteries, potentially related to hyperviscosity (Figure 1F). The only observation was the administration of intranasal vasoconstrictor therapy the evening before, however the causal relationship was not confirmed.

**Long-term Treatment and Outcome**

Excepting the patient with a DHTTR, all patients received monthly exchange transfusions for at least 6 months after the acute phase.

Among the surviving 10 patients 12 months after the stroke, 100% of children with “typical” stroke were still receiving monthly exchange transfusions, whereas 40% (4/10) of the children with “atypical” stroke were considered that they no longer required exchange transfusions as MRA was normal (Figure 3). One child in this group was lost to follow-up.

Two years after the stroke, all but one patient with a “typical” stroke were still receiving exchange transfusions due to persistent cerebral arterial stenosis. One patient stopped the exchange transfusions because of bone marrow transplantation.

In the “atypical” stroke group, 2 years after the stroke, 70% (7/10) of the children were no longer receiving exchange transfusions (Figure 3). The 3 remaining patients were still receiving monthly exchange transfusions due to corticosteroid-dependent nephrotic syndrome in one case, occurrence of stroke on HU therapy with elevated Hb with no other apparent contributing factors for one case, and appearance of SCD-related CA contralateral to the ischemic territory in the last case. Among the 7 patients who stopped the transfusion program, 4 received, or continued to receive, treatment with hydroxyurea, the other 3 children had SC genotype.

Overall, the rate of neurological sequelae was similar in the 2 groups with motor deficiency in 65% of patients and cognitive impairment in 61%. No recurrence of stroke was observed in the “atypical” stroke group, including for the patients who had stopped the transfusion program, whereas 38% (n=5) of the patients with “typical” stroke had a further stroke in the following 2 years despite monthly exchange transfusion. This high rate of stroke recurrence is consistent with the high prevalence of Moya-Moya in this group (61% (8/13). All the five children who had a recurrence of stroke had Moya-Moya underlying the strong correlation between Moya-Moya and risk of recurrence of stroke in SCD 17.

**Discussion**

Cerebral arteriopathy, described as stenosis of one or more cerebral arteries in the circle of Willis occurring in children with SCA between 2 and 15 years of age, is known to be the main etiology of ischemic stroke in SCD patients. Nevertheless, our study shows that ischemic stroke can also occur in children with SCD with genotypes other than SS or Sβ, and in patients without “typical” CA. In the past 15 years in our referral SCD center, almost half of the strokes in SCD children were due to an etiology other than SCD-associated CA, which led us to question the circumstances of these strokes, their etiologies, the patients at risk and the appropriate long-term treatments.

The prevalence of stroke in our cohort is low compared to the number of patients followed in our SCD Referral Center, i.e. 25 strokes in 15 years in an active database of around 1300 patients per year. Similarly, the proportion of strokes without CA may appear high at 12/25 cases, however the two results can be explained by
the routine implementation of preventive measures to screen for CA, which has drastically reduced the number of strokes due to undiagnosed CA in SCA children over the past 15 years. Paradoxically, this highly effective strategy for reducing the risk of stroke in children with SCA highlights the risk of stroke in other patients with SCD, where it is more difficult to prevent. As regards the profile of pre-stroke patients, on the whole they are patients with a mild disease (4% had more than 3 hospitalized VOC in the past 12 months and 28% had a treatment with Hydroxyurea). The only criterion of severity we found surprisingly high was the rate of history of acute splenic sequestration (44% in the whole cohort of patients, 58% in the group with “atypical” vasculopathy). Recently, our group published the consequence of early splenectomy in a large cohort of children with SCA and showed an increased proportion of cerebral vasculopathy in children with early splenic dysfunction and splenectomized before 3 years old. This relation between splenic dysfunction and neurological complications in children should probably be further investigated.

Apart from those with CA, which children with SCD are at risk for stroke?

The first conclusion of our study is that stroke without CA can occur in children older than expected, with a median 9 years of age and maximum 15 years old in our study. As expected, patients with SCA had the highest risk of stroke, but stroke can also occur in patients with SC genotype, 3/12 in our study. The second important observation is that 58% of the children in the “atypical” stroke group were currently hospitalized in the ICU for another reason at stroke onset or had been in the previous week. This suggests that stroke onset in children with SCD can follow a recent medical event in SCD children with a low risk of stroke. Particular clinical conditions such as corticosteroid therapy, severe infections or severe pulmonary dysfunctions represented half of the secondary stroke settings in our study, even after efficient transfusion therapy leading to HbS levels below 30%.

For various reasons, children with SCD have a lower cerebrovascular reserve compared to healthy controls, i.e. a reduced capacity of their cerebral vessels to dilate in response to increased requirements. Moreover, SCD is characterized by basal endothelial dysfunction related to chronic inflammation, which promotes long-term vascular wall thickening and, potentially, inappropriate vascular response. The ischemic lesions observed in our study may be due to local phenomena affecting cerebral blood flow through vascular wall damage and/or arterial obstruction, often in a systemic context that itself promotes cerebral hypoperfusion (acute anemia or acute hypoxia). Conversely, increased blood viscosity was suspected to be implicated in 2 cases of stroke in our study and has been reported as responsible for complications in SCD. Given the underlying vascular dysfunction, impaired microcirculation may be unable to compensate for a rapid increase in Hb level by increasing vascular resistance and promoting RBC aggregation. In addition, major hyperleukocytosis promoted by inflammation or corticosteroid therapy may increase blood viscosity. Involvement of leukocytes, particularly neutrophils in vascular and organ damage in SCD patients is well described beyond 20 x10⁹/L, including in stroke. Inflammation could also promote increased adhesion of white blood cells to the endothelial wall, contributing to reduced blood flow and vascular damage.

Necrosis of bone marrow in the long bones adds an embolic risk of another nature via the cerebral fat embolism syndrome. It follows the release into the systemic circulation of fatty lobules associated with extensive bone marrow infarction. Classically, patients in this situation present with signs of respiratory failure and encephalopathy associated with pancytopenia. In the majority of cases (80%), patients have a non-SS genotype. A background of parvovirus B19 infection is found in 24% of cases in patients with SCD and fat embolism.

Among our patients with “atypical” stroke, we identified two cases of RCVS, a rare vascular disorder of imperfectly understood etiology, characterized by diffuse sudden vasoconstriction of the cerebral arterial vasculature, sometimes associated with neurological deficits due to hemorrhage or infarct, and spontaneously reversible in 1 to 3 months. The best described predisposing factors are physical exercise, immersion in cold water, Valsalva maneuver (forced expiration with closed glottis) or vasoconstrictor treatment. In SCD, several underlying risk factors may increase the risk of RCVS such as blood viscosity fluctuations, disrupted regulation of the vascular tone and endothelial dysfunction. Transfusion is also an identified risk factor in SCD children as are corticosteroids and immunomodulatory therapies. Last, exposure to cannabinoids, known to be a potential trigger, should be considered in case of RCVS in SCD patient.

Overall, this suggests that, in the absence of CA, SCD itself, its complications and sometimes the therapies required may be additional factors for stroke in these patients. Any SCD child who experiences a variation in
blood viscosity, acute severe inflammatory reaction or hypotension should be considered as at risk of ischemic stroke.

What long-term treatment for SCD children with stroke without CA?

In accordance with guidelines, all patients were managed in the acute phase to reduce HbS below 30%, regardless of the presumed mechanism of the stroke or the SCD genotype, in order to improve cerebral perfusion. In the same perspective, in the absence of consensus guidelines, antiplatelet therapy was added when platelet levels were > 450 x10⁹/L in all the patients in our cohort and in both groups, to prevent thrombotic complications.

In patients without arterial stenosis, the rationale of maintaining a long-term transfusion program may be questioned. During the first 6 months, we considered that the benefit of long-term exchange transfusion, by maintaining an HbS rate below 30% and a total Hb level around 10 g/dL, was to facilitate the recovery of the cerebral parenchyma, and to limit neurological sequelae. Thus, taking into account the transient nature of the precipitating factors as well as potential adverse effects and constraints of this therapy, in most of the patients in the “atypical” stroke group, we decided to interrupt the transfusion program when arterial stenosis or other identified risk factors for stroke recurrence were absent.

No acute neurological events were reported in the 24 months following the stroke in the cohort of patients with “atypical” strokes whereas, in the “typical” stroke group, recurrent seizures were reported in 46% of patients (p=0.045) and recurrent strokes in 38% (p=0.034) despite the continuation of exchange transfusion programs. The risk of stroke recurrence is known to be very high in children with CA in the absence of transfusion program, however our small descriptive study suggests that, following “atypical” stroke, exchange transfusions can be stopped on a case-by-case basis, with no major risk of recurrence. Nevertheless, Hydroxyurea treatment should be systematically considered for these patients, in order to prevent future complications that may again lead to atypical stroke.

Conclusion

Although CA is the main etiology of ischemic stroke in children with SCA, at least in those who do not receive primary stroke prevention, the occurrence of stroke without arterial stenosis in SCD children is not rare, particularly in adolescents and HbSC patients. These atypical strokes have been happening all along, but they were probably missed or under-appreciated or, before the advent of an effective stroke prevention strategy, they constituted a minority of events and were wrongly attributed to sickle cell-specific causes. Nevertheless, even in the absence of CA, SCD seems to be a favorable terrain for other stroke etiologies in children, which need to be explored and specifically treated. Finally, even if silent ischemic strokes were not the subject of this study, they fall within the scope of frequent ischemic phenomena, the etiology of which remains uncertain. The same pathological processes should be considered to explain them.

Atypical strokes seem to be facilitated by severe complications related to SCD. In the absence of specific guidelines, we suggest that any factors favoring hyperviscosity, thrombosis or low cerebral blood flow should alert physicians to the risk of stroke in a child with SCD. In secondary prevention, after the acute phase, stopping exchange transfusion programs does not seem to increase the risk of stroke recurrence. In the absence of arterial cerebral stenosis, continuation of long-term transfusion programs should be discussed on a case-by-case basis in order to avoid side effects associated with chronic transfusions.
References


Table 1. Demographic, clinical and laboratory parameters at baseline

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<tr>
<th>Sex ratio (F/M)</th>
<th>All (n=25)</th>
<th>Atypical (n=12)</th>
<th>Typical (n=13)</th>
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<td>1.08 (13/12)</td>
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<tr>
<td>SS/Sb&lt;sup&gt;1&lt;/sup&gt;</td>
<td>22 (88%)</td>
<td>9 (75%)</td>
<td>13 (100%)</td>
<td>0.09</td>
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<td>SC</td>
<td>3 (12%)</td>
<td>3 (25%)</td>
<td>0 (0%)</td>
<td>0.09</td>
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| G6PD deficit | 2 (8%) | 1 (8%) | 1 (8%) | 1       |

| Neurological history<sup>a</sup> | 4 (16%) | 3 (25%) | 1 (8%) | 0.32    |

| >3 hospitalized VOCs<sup>b</sup> in the 12 months prior to stroke | 1 (4%) | 1 (8%) | 0 | 0.48    |

| >1 history of acute chest syndrome | 9 (36%) | 6 (50%) | 3 (23%) | 0.21    |

| Asthma | 6 (24%) | 4 (33%) | 2 (15%) | 0.38    |

| History of ≥1 episode of acute splenic sequestration | 11 (44%) | 7 (58%) | 4 (31%) | 0.21    |

| Hydroxyurea treatment for at least 3 months | 7 (28%) | 5 (42%) | 2 (15%) | 0.20    |

| Chronic transfusion therapy at the time of the stroke<sup>c</sup> | 1 (4%) | 0 | 1 (8%) | 0.48    |

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<th>Baseline laboratory parameters (median [IQR]):</th>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>7.9 [7.2–9.3]</td>
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<td>7.4 [6.8–8.1]</td>
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<tr>
<td>Leucocyte count (10&lt;sup&gt;9&lt;/sup&gt;/L)</td>
<td>15.3 [10.2–16.7]</td>
<td>11.3 [8.9–15]</td>
<td>15.8 [13.9–17.5]</td>
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<td>Fetal hemoglobin (%)</td>
<td>10.1 [5.3–15.5]</td>
<td>6.2 [3–10.6]</td>
<td>13.7 [10.4–19.3]</td>
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</tr>
<tr>
<td>Lactate dehydrogenase (IU/L)</td>
<td>895 [137–1218]</td>
<td>895 [584–1293]</td>
<td>1236 [1193–1537]</td>
<td>0.16</td>
</tr>
<tr>
<td>ASAT (IU/L)</td>
<td>56 [32–64]</td>
<td>56 [42–69]</td>
<td>60 [56–64]</td>
<td>0.90</td>
</tr>
</tbody>
</table>

<sup>a</sup> Psychomotor delay, seizures, meningitis or encephalitis

<sup>b</sup> Vaso-occlusive crisis

<sup>c</sup> Recurrent transfusions or exchange transfusions for sickle CA at the time of the stroke
Table 2. Clinical and biological status at stroke onset

<table>
<thead>
<tr>
<th></th>
<th>All (n=25)</th>
<th>Atypical (n=12)</th>
<th>Typical (n=13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at stroke onset (median [IQR])</td>
<td>6.6 [3.3–9.3]</td>
<td>9.0 [4.2–14.2]</td>
<td>3.6 [2.9–7.8]</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Stroke presentation n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Motor deficit</td>
<td>19 (76%)</td>
<td>8 (67%)</td>
<td>11 (85%)</td>
<td>0.38</td>
</tr>
<tr>
<td>- Headache</td>
<td>7 (28%)</td>
<td>3 (25%)</td>
<td>4 (31%)</td>
<td>1</td>
</tr>
<tr>
<td>- Seizures</td>
<td>9 (36%)</td>
<td>4 (33%)</td>
<td>5 (38%)</td>
<td>1</td>
</tr>
<tr>
<td>- Impaired consciousness</td>
<td>4 (16%)</td>
<td>2 (17%)</td>
<td>2 (15%)</td>
<td>1</td>
</tr>
<tr>
<td>Context of stroke occurrence n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hospitalized in the ICU the previous week for a reason other than stroke</td>
<td>8 (32%)</td>
<td>7 (58%)</td>
<td>1 (8%)</td>
<td>*0.011</td>
</tr>
<tr>
<td>- IV corticosteroids in the last 7 days</td>
<td>4 (16%)</td>
<td>3 (25%)</td>
<td>1 (8%)</td>
<td>0.32</td>
</tr>
<tr>
<td>- Acute chest syndrome in the last 15 days</td>
<td>3 (12%)</td>
<td>2 (17%)</td>
<td>1 (8%)</td>
<td>0.59</td>
</tr>
<tr>
<td>- Acute anemia a</td>
<td>3 (12%)</td>
<td>2 (17%)</td>
<td>1 (8%)</td>
<td>0.59</td>
</tr>
<tr>
<td>- Acute splenic sequestration</td>
<td>1 (4%)</td>
<td>0</td>
<td>1 (8%)</td>
<td>1</td>
</tr>
<tr>
<td>- Fever</td>
<td>9 (36%)</td>
<td>5 (42%)</td>
<td>4 (31%)</td>
<td>0.69</td>
</tr>
<tr>
<td>- Vaso-occlusive crisis</td>
<td>3 (12%)</td>
<td>2 (17%)</td>
<td>1 (8%)</td>
<td>0.59</td>
</tr>
<tr>
<td>- Elevated blood pressure b</td>
<td>2 (8%)</td>
<td>2 (17%)</td>
<td>0</td>
<td>0.22</td>
</tr>
<tr>
<td>- Nephrotic syndrome</td>
<td>2 (8%)</td>
<td>2 (17%)</td>
<td>0</td>
<td>0.22</td>
</tr>
<tr>
<td>- Physical effort</td>
<td>1 (4%)</td>
<td>1 (8%)</td>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>- Cranial trauma</td>
<td>1 (4%)</td>
<td>0</td>
<td>1 (4%)</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory parameters in the first 24 hrs after stroke onset (median [IQR])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HbS (%)</td>
<td>64 [45–79]</td>
<td>50 [26–66]</td>
<td>78 [50–86]</td>
<td>0.076</td>
</tr>
<tr>
<td>- Hemoglobin (g/dL)</td>
<td>8.6 [7.0–11.4]</td>
<td>11 [7.4–12.6]</td>
<td>7.4 [6.6–9.1]</td>
<td>*0.027</td>
</tr>
<tr>
<td>- Hemoglobin &gt; 10.5 g/dL (n (%))</td>
<td>7 (28%)</td>
<td>7 (58%)</td>
<td>0</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>- Platelets (10⁹/L)</td>
<td>325 [272–468]</td>
<td>325 [197–461]</td>
<td>353 [279–471]</td>
<td>0.68</td>
</tr>
<tr>
<td>- ASAT (IU/L)</td>
<td>62 [50–106]</td>
<td>91 [50–135]</td>
<td>58 [48–61]</td>
<td>0.09</td>
</tr>
</tbody>
</table>

a Decrease of at least 2 g/dL compared to the baseline hemoglobin level

b Occurred in the context of corticosteroid therapy for DTH in one patient and nephrotic syndrome in another patient
<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Genotype</th>
<th>HU*</th>
<th>Context</th>
<th>Clinical features</th>
<th>Vascular territory of stroke</th>
<th>MRA findings</th>
<th>Mechanism</th>
<th>Acute management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>39 yo</td>
<td>SP*</td>
<td>No</td>
<td>DHTR</td>
<td>Headache, seizures, R. hemiplegia</td>
<td>L. internal frontal-parietal infarction + ischemic lesions of the cerebellar lobes</td>
<td>Irregularities in the arteries of the circle of Willis and the basilar artery</td>
<td>ROVS</td>
<td>Exchange transfusion</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>92 yo</td>
<td>SC</td>
<td>No</td>
<td>Short general anesthesia</td>
<td>Status epilepticus and L. hemiplegia</td>
<td>Bilateral frontal and parieto-occipital ischemic lesions [R &gt; L]</td>
<td>Irregularities in the arteries of the circle of Willis and the basilar artery</td>
<td>ROVS</td>
<td>Exchange transfusion</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>12.7 yo</td>
<td>SS</td>
<td></td>
<td>Nephrotic syndrome</td>
<td>Seizures, aphasia and R. hemiplegia</td>
<td>Total L. MCA infarction + ischemic lesion of the R. caudate nucleus</td>
<td>Occlusion of both carotid siphons + L. middle cerebral artery + L. anterior cerebral artery</td>
<td>Arterial thrombosis</td>
<td>Exchange transfusion – corticosteroid + anti-coagulation</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>8.9 yo</td>
<td>SS</td>
<td>Yes</td>
<td>ARDS</td>
<td>L. areflexic mydriasis and absence of brainstem reflexes (intubated child)</td>
<td>Posterior territories infarction + tonsillar hernia + active hydrocephalus</td>
<td>Occlusion of basilar artery</td>
<td>Arterial thrombosis</td>
<td>Non specific [exchange transfusion 8 days before]</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>15.2 yo</td>
<td>SS</td>
<td>Yes</td>
<td>VOC</td>
<td>L. hemiplegia</td>
<td>R. MCA infarction [deep superficial territory]</td>
<td>Normal</td>
<td>Arterial thrombosis</td>
<td>Exchange transfusion</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>3.9 yo</td>
<td>SS</td>
<td>Yes</td>
<td>ARDS</td>
<td>L. hemiplegia</td>
<td>R. MCA infarction [deep territory]</td>
<td>Normal</td>
<td>Thromboembolism</td>
<td>Non specific [exchange transfusion 6 days before]</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>14.8 yo</td>
<td>SS</td>
<td>No</td>
<td>Effort</td>
<td>Cerebellar syndrome</td>
<td>L. cerebellar ischemic lesion</td>
<td>Normal</td>
<td>Thromboembolism</td>
<td>Exchange transfusion – antiplatelet</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>14.6 yo</td>
<td>SC</td>
<td>No</td>
<td>Unidentified trigger, hemostatic 35%</td>
<td>Aphasias, R. hemiplegia</td>
<td>L. MCA infarction [deep territory]</td>
<td>Normal</td>
<td>Hypercoagulability</td>
<td>Exchange transfusion</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>28 yo</td>
<td>SS</td>
<td>No</td>
<td>Nephrotic syndrome, elevated blood pressure, hemostatic 38%</td>
<td>Impaired consciousness and L. hemiplegia</td>
<td>Ischemic lesions of the centrum semiovale [R &gt; L]</td>
<td>Normal</td>
<td>Hypercoagulability</td>
<td>Exchange transfusion – corticosteroid</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>13 yo</td>
<td>SC</td>
<td>No</td>
<td>Parvovirus B19 infection, bone marrow necrosis</td>
<td>Impaired consciousness and seizures</td>
<td>Multiple ischemic lesions of the subcortical and infratentorial white matter and basal ganglia</td>
<td>Normal</td>
<td>Cerebral fat embolism syndrome</td>
<td>Transfusion</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>8.2 yo</td>
<td>SS</td>
<td>Yes</td>
<td>Septic shock, pneumococcal meningitis; encephalitis</td>
<td>Headache then reactive coma with opalescent boluses</td>
<td>Infarction of the L. MCA and posterior vascular territories + L. cerebellar lesions + meningeal enhancement</td>
<td>Normal</td>
<td>Meningoencephalitis associated vasculopathy</td>
<td>Transfusion – antibiotics</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>5.1 yo</td>
<td>SS</td>
<td>Yes</td>
<td>VOC</td>
<td>Seizures with subsequent hypotension requiring volume resuscitation</td>
<td>Ischemic lesion of the R. parieto-occipital white matter</td>
<td>Normal</td>
<td>Acute low cerebral blood flow</td>
<td>Exchange transfusion</td>
</tr>
</tbody>
</table>

* Taking hydroxyurea before stroke; HU*: Hydroxyurea; MRA: Magnetic Resonance Angiography; DHTR: Delayed hemolysis post-transfusion reaction; ROVS: Reversible cerebral vasospasm syndrome; ARDS: Acute respiratory distress syndrome; VOC: Vasococlusive crisis; yo: years old; L: Left; R: Right; MCA: Middle Cerebral artery
**Figure 1:** Representative brain Magnetic Resonance Imaging of various etiologies for ischemic stroke in children sickle cell disease with no sickle-related cerebral arteriopathy (Panel A to F)

**A:** Reversible cerebral vasoconstriction syndrome (Patient 1)
A1: Axial supratentorial view in diffusion weighted imaging (DWI) sequence showing left medial parietal-occipital lesion. A2: Axial infratentorial DWI view with focal lesions in both cerebellar lobes.

**B:** Cerebral fat embolism syndrome (Patient 10)

**C:** Arterial thrombosis (Patient 3)
C1: Axial DWI view, C2: Axial view of apparent diffusion coefficient map (ADC). Acute ischemic lesions in the complete left MCA territory and of the head of the right caudate nucleus and right frontal deep white matter.

**D:** Cerebral vasculitis complicating pneumococcal meningoencephalitis (Patient 11)
D1: Axial DWI view. Ischemic lesion in the left posterior cerebral artery territory. D2: axial SWI infratentorial view showing numerous petechiae predominating in the left cerebellar lobe.

**E:** Low cerebral blood flow (Patient 12)
Axial DWI view: small foci of DWI hyperintensity in the right parietal-occipital white matter.

**F:** Hyperviscosity (Patient 8)
F1: Axial FLAIR view, F2: Axial ADC view. Ischemia in the left deep MCA territory.

**Figure 2:** Course of ischemic stroke and vascular aspect on representative Magnetic Resonance Imaging and Magnetic Resonance Angiography in patients with no sickle-related arteriopathy (Panel G and H)

**A:** Reversible cerebral vasoconstriction syndrome (Patient 1)
A1: MRI at the time of stroke. Axial DWI supratentorial view showing left medial ACA territory infarct extending to the posterior cerebral artery territory; A2: 3D time of flight (TOF) MRA: multifocal segmental narrowing involving all cerebral arteries bilaterally (some are indicated with red arrows).

**B:** Arterial thrombosis (Patient 3)
B1: Head CT without contrast at the acute phase of stroke: large thrombus seen as a spontaneous hyperdensity of the terminal left internal carotid artery and the left middle cerebral artery. B2: MRI at the time of stroke. Axial FLAIR view showing acute infarct in the complete left MCA territory, the head of the right caudate nucleus and the right frontal deep white matter. B3: on TOF MRA absence of visualization of internal carotid arteries, left ACA first segment and left MCA. Basilar artery compensatorily supplies the right middle cerebral artery and the anterior cerebral arteries through the Willis anastomoses.
B4: MRI 1 year after the stroke: Axial FLAIR view showing ventricular dilatation, necrosis, atrophy and cavitation of the left cerebral parenchyma. B5: on MRA, recovery of perfusion of the terminal segment of the left internal carotid artery and the proximal segment of the left MCA and ACA. Development of collateral circulation pathways from the external carotid arteries.

**Figure 3:** Follow-up within 24 months of stroke: duration of exchange transfusion program and stroke recurrence in the two groups