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

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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 of 1,500 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 more frequently had SC genotype (25% *vs*. 0%, respectively). Their strokes more frequently involved the posterior circulation, 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 meningo-encephalitis, and severe hemodynamic failure. No recurrence was observed in the 24 months following stroke, even though 67% of the patients in this group were no longer receiving exchange transfusions. In conclusion, in a cohort of pediatric SCD patients with an efficient stroke screening strategy, half of the ischemic strokes that occurred 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 (CA) 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 period of 9 years in the 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 imaging (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 been 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 CA 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 diagnoses 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 1,300 children with SCD. All patients with SCA (homozygous or Sβ^0 genotype) undergo routine annual TCD from 18-24 months of age. If the TCD is abnormal, cerebral MRI is performed to complete the neurological screening. In accordance with international recommendations, patients with abnormal TCD are re-evaluated in the next 3 months and, in the event of persistent abnormality or pathological Doppler (>200 cm/s), transfusion therapy is promptly initiated. Around 15% of the patients in our SCD cohort have the SC genotype and are not involved in the routine screening for cerebral vasculopathy, as recommended.[11]

In this study, we retrospectively analyzed data from all patients with SCD (any genotype), aged 0-18 years 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 CA is a chronic CA involving the anterior circulation, in this study only arteriopathies involving an internal carotid artery, middle cerebral artery or anterior cerebral artery and with persisting MRA or TCD abnormality at 3 months after the stroke[16] were labeled SCD-CA. Stroke was thus termed as "typical" if (i) associated with SCD-related CA (SCD-CA) and (ii) located in the cerebral territory of the 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. All the results of the statistical analyses 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), the stroke was considered as "typical" in the context of SCD. Although all of them were theoretically eligible for routine screening for CA, six of the 13 patients had not actually undergone TCD in the preceding 12 months: four were lost to follow-up, one had just arrived from Africa and one had failed to undergo adequate cerebral blood flow measurement on TCD because of narrow temporal windows. Among the seven patients with proper screening for CA, six 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-CA was not met and the stroke was classified as "atypical". In this group, in the nine of 12 patients who were eligible for routine screening for CA, i.e. patients with SS and Sβ^0 genotype, seven had normal TCD and/or cerebral MRI findings in the 12 months before the stroke occurred. For the two patients without brain imaging in the preceding 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" strokes, 25% *versus* 0% in the group with "typical" stroke. The main baseline characteristics of the 25 patients prior to their strokes are presented in Table 1.

Considering biological parameters, we observed a lower leukocyte count and a lower percentage of fetal hemoglobin (HbF) in the group with "atypical" strokes compared to the group with "typical" strokes ($11.3x10^9$/L *vs*. $15.8x10^9$/L, $P=0.04$ and 6.2% *vs*. 13.2% $P=0.01$, respectively), probably related to the older age and higher proportion of children with SC genotype in the "atypical" stroke group.

Stroke characteristics

The median age at stroke onset was significantly higher in the group with "atypical" strokes than in the group with "typical" strokes, being 9.0 years of age *versus* 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, seven of the 12 strokes (58%) occurred during or shortly after a hospital stay in the intensive care unit (ICU) for delayed hemolytic transfusion reaction (n=1), severe parvovirus B19 infection with bone marrow necrosis and macrophage activation syndrome (n=1), severe acute chest syndrome (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 one child was in the ICU at stroke onset, the reason being acute chest syndrome. Notably, three children in the "atypical" stroke group had received intravenous corticosteroids during the 2 weeks preceding the stroke compared to only one in the "typical" stroke group. The symptoms accompanying the event, i.e. hypoxia, acute anemia, fever, and vaso-occlusive crisis did not differ between the two groups. Stroke characteristics are summarized in Table 2. Laboratory assessments showed that in the "atypical" stroke group, hemoglobin levels at the time of the 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 hemoglobin 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" strokes had ischemic lesions in the territory of the anterior cerebral circulation and 100% of them had, by definition, arterial stenosis in an artery upstream of the ischemic territory on three-dimensional, 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.

Table 1. Demographic, clinical and laboratory parameters at baseline.

	All N=25	Atypical N=12	Typical N=13	*P*
Sex ratio (F/M)	1.08 (13/12)	8/4	5/8	0.23
Genotype, N (%)				
SS/Sβ^0	22 (88)	9 (75)	13 (100)	0.09
SC	3 (12)	3 (25)	0 (0)	0.09
G6PD deficiency, N (%)	2 (8)	1 (8)	1 (8)	1
Neurological history, N (%)[a]	4 (16)	3 (25)	1 (8)	0.32
>3 hospital admissions for VOC in the 12 months prior to stroke, N (%)	1 (4)	1 (8)	0	0.48
History of >1 episodes of acute chest syndrome, N (%)	9 (36)	6 (50)	3 (23)	0.21
Asthma, N (%)	6 (24)	4 (33)	2 (15)	0.38
History of ≥1 episode of acute splenic sequestration, N (%)	11 (44)	7 (58)	4 (31)	0.21
Hydroxyurea treatment for at least 3 months, N (%)	7 (28)	5 (42)	2 (15)	0.20
Chronic transfusion therapy at the time of the stroke, N (%)[b]	1 (4)	0	1 (8)	0.48
Baseline laboratory parameters, median (IQR)				
Hemoglobin, g/dL	7.9 (7.2-9.3)	8.6 (7.2-10.7)	7.4 (6.8-8.1)	0.13
Hematocrit, %	21 (21-23)	23 (20-31)	21 (20-21)	0.22
Leukocyte count x10^9/L	13.3 (10.2-16.7)	11.3 (8.9-15)	15.8 (13.9-17.5)	0.04
Platelet count x10^9/L	321 (223-418)	370 (252-480)	326 (315-360)	0.86
Reticulocyte count x10^9/L	248 (162-386)	220 (164-432)	325 (282-386)	0.30
Fetal hemoglobin, %	10.1 (5.3-15.5)	6.2 (3-10.6)	13.2 (10.4-19.3)	0.02
Lactate dehydrogenase, IU/L	895 (137-1,218)	895 (584-1,293)	1,226 (1,193-1,537)	0.16
ASAT, IU/L	56 (32-64)	56 (42-69)	60 (56-64)	0.90
Free bilirubin, μmol/L	25 (17-41)	33 (17-102)	25 (21.5-42)	0.91

[a]Psychomotor delay, seizures, meningitis or encephalitis. [b]Recurrent transfusions or exchange transfusions for sickle cerebral arteriopathy at the time of the stroke. F: female; M: male; G6PD: glucose-6-phosphate deficiency; VOC: vaso-occlusive crisis; IQR: interquartile range; ASAT: aspartate aminotransferase.

In the "atypical" stroke group, arterial abnormalities on three-dimensional, time-of-flight MRA were observed in four of the 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 eight 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 of "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 a "typical" stroke related to CA in SCD.

If not, various other etiological mechanisms of stroke were discussed in multidisciplinary team meetings. Overall, six different diagnoses were put forward for the 12 patients with "atypical" stroke (see Table 3, with a selection of relevant images 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; it is associated with acute "thunderclap" headaches with multifocal alternation of segmental narrowing and dilatation of the cerebral arteries on angiography (MRA, computed tomography angiography 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) was a 4-year-old girl with $S\beta^0$ SCA hospitalized in the ICU for a delayed hemolytic transfusion reaction. Because of a very low hemoglobin level, she received a red blood cell transfusion and combined treatment with corticosteroids and eculizumab to limit the risk of a recurrence of the hemolytic transfusion reaction, increasing her hemoglobin level from 2.7 g/dL to 9 g/dL. She experienced a stroke 6

Table 2. Clinical and biological status at stroke onset.

	All N=25	Atypical N=12	Typical N=13	*P*
Age in years at stroke onset, median (IQR)	6.6 (3.3-9.3)	9.0 (4.2-14.2)	3.6 (2.9-7.8)	0.008
Stroke presentation, N (%)				
Motor deficit	19 (76)	8 (67)	11 (85)	0.38
Headache	7 (28)	3 (25)	4 (31)	1
Seizures	9 (36)	4 (33)	5 (38)	1
Impaired consciousness	4 (16)	2 (17)	2 (15)	1
Context of stroke occurrence, N (%)				
Hospitalized in the ICU the previous week for a reason other than stroke	8 (32)	7 (58)	1 (8)	0.011
IV corticosteroids in the preceding 7 days	4 (16)	3 (25)	1 (8)	0.32
Acute chest syndrome in the preceding 15 days	3 (12)	2 (17)	1 (8)	0.59
Acute anemia[a]	3 (12)	2 (17)	1 (8)	0.59
Acute splenic sequestration	1 (4)	0	1 (8)	1
Fever	9 (36)	5 (42)	4 (31)	0.69
Vaso-occlusive crisis	3 (12)	2 (17)	1 (4)	0.59
Elevated blood pressure[b]	2 (8)	2 (17)	0	0.22
Nephrotic syndrome	2 (8)	2 (17)	0	0.22
Physical effort	1 (4)	1 (8)	0	0.48
Cranial trauma	1 (4)	0	1 (4)	1
Laboratory parameters in the first 24 hrs after stroke onset, median (IQR)				
HbS, %	64 (45-79)	50 (26-66)	78 (50-86)	0.076
Hemoglobin, g/dL	8.6 (7.0-11.4)	11 (7.4-12.6)	7.4 (6.6-9.1)	0.027
Hemoglobin >10.5 g/dL, N (%)	7 (28)	7 (58)	0	0.001
Hematocrit, %	25 (21-29)	29 (23-35)	22 (20-25)	0.017
Leukocytes $x10^9$/L	15.2 (10.7-22.9)	13.9 (10.2-21)	16.5 (13.7-26.2)	0.065
Platelets $x10^9$/L	325 (272-468)	325 (197-461)	353 (279-471)	0.68
ASAT, IU/L	62 (50-106)	91 (50-135)	58 (48-61)	0.09
Free bilirubin, μmol/L	27 (14-37)	29 (11-37)	26 (20-43)	0.77

[a]Decrease of at least 2 g/dL compared to the baseline hemoglobin level. [b]Occurred in the context of corticosteroid therapy for delayed hemolytic transfusion reaction in one patient and nephrotic syndrome in another patient. IQR: interquartile range; ICU: Intensive Care Unit; ASAT: aspartate aminotransferase.

Table 3. Description of the cases of "atypical" stroke.

N/Sex Age	Genotype	HU[a]	Context	Clinical features	Vascular territory of stroke	MRA findings	Mechanism	Acute management
1/F 3.9 yrs	Sβ^0	No	DHTR	Headache, seizures, R. hemiplegia	L. internal frontal-parietal infarction + ischemic lesions of the cerebellar lobes	Irregularities in the arteries of the circle of Willis and the basilar artery	RCVS	Exchange transfusion
2/F 9.2 yrs	SC	No	Short general anesthesia	Status epilepticus and L. hemiplegia	Bilateral frontal and parietal-occipital ischemic lesions (R. > L.)	Irregularities in the arteries of the circle of Willis and the basilar artery	RCVS	Exchange transfusion
3/F 12.7 yrs	SS	No	Nephrotic syndrome	Seizures, aphasia and R. hemiplegia	Total L. MCA infarction + ischemic lesion of the R. caudate nucleus	Occlusion of both carotid siphons + L. middle cerebral artery + L. anterior cerebral artery	Arterial thrombosis	Exchange transfusion - corticosteroid + anticoagulation
4/M 8.9 yrs	SS	Yes	ARDS	L. areactive mydriasis and absence of brainstem reflexes (intubated child)	Posterior territories infarction + tonsillar hernia + active hydrocephalus	Occlusion of basilar artery	Arterial thrombosis	Non-specific (exchange transfusion 8 days before)
5/M 15.2 yrs	SS	Yes	VOC	L. hemiplegia	R. MCA infarction (deep and superficial territories)	Normal	Arterial thrombosis	Exchange transfusion
6/F 3.9 yrs	SS	Yes	ARDS	L. hemiplegia	R. MCA infarction (deep territory)	Normal	Thrombo-embolism	Non-specific (exchange transfusion 6 days before)
7/F 14.9 yrs	SS	No	Effort	Cerebellar syndrome	L. cerebellar ischemic lesion	Normal	Thrombo-embolism	Exchange transfusion - antiplatelet
8/F 14.6 yrs	SC	No	Unidentified trigger, hematocrit 35%	Aphasia, R. hemiplegia	L. MCA infarction (deep territory)	Normal	Hyperviscosity	Exchange transfusion
9/M 2.8 yrs	SS	No	Nephrotic syndrome, elevated blood pressure, hematocrit 38%	Impaired consciousness and L. hemiplegia	Ischemic lesions of the centrum semiovale (R. > L.)	Normal	Hyperviscosity	Exchange transfusion - corticosteroid
10/F 13 yrs	SC	No	Severe parvovirus B19 infection, bone marrow necrosis	Impaired consciousness and seizures	Multiple ischemic lesions of the supra- and infratentorial white matter and basal ganglia	Normal	Cerebral fat embolism syndrome	Transfusion
11/F 8.2 yrs	SS	Yes	Septic shock, pneumococcal meningo-encephalitis	Headache then areactive coma with opisthotonos	Infarction of the L. MCA and posterior vascular territories + L. cerebellar lesions + meningeal enhancement	Normal	Meningo-encephalitis associated vasculopathy	Transfusion - antibiotics
12/M 5.1 yrs	SS	Yes	VOC	Seizures with subsequent hypotension requiring volume resuscitation	Ischemic lesion of the R. parietal-occipital white matter	Normal	Acute low cerebral blood flow	Exchange transfusion

[a]Taking hydroxyurea before stroke. HU: hydroxyurea; MRA: magnetic resonance angiography; F: female; yrs: years; DHTR: delayed hemolytic post-transfusion reaction; R: right; L: left; RCVS: reversible cerebral vasoconstriction syndrome; MCA: middle cerebral artery; M: male; ARDS: acute respiratory distress syndrome; VOC: vaso-occlusive crisis.

days later. Cerebral and angiographic imaging was compatible with RVCS (Figures 1A and 2A). The second case (patient 2; Table 3) was 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 hemoglobin level at 13 g/dL from a baseline of 10 g/dL (Table 3). High blood pressure was present at stroke onset in patient 1 but only the day after the stroke 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 with SC genotype who had a stroke during hospitalization for severe primary infection with parvovirus B19 complicated by acute bone marrow necrosis.

In five cases, thrombosis or thromboembolism was diagnosed (patients 3 to 7; Table 3, Figures 1C and 2B). All five

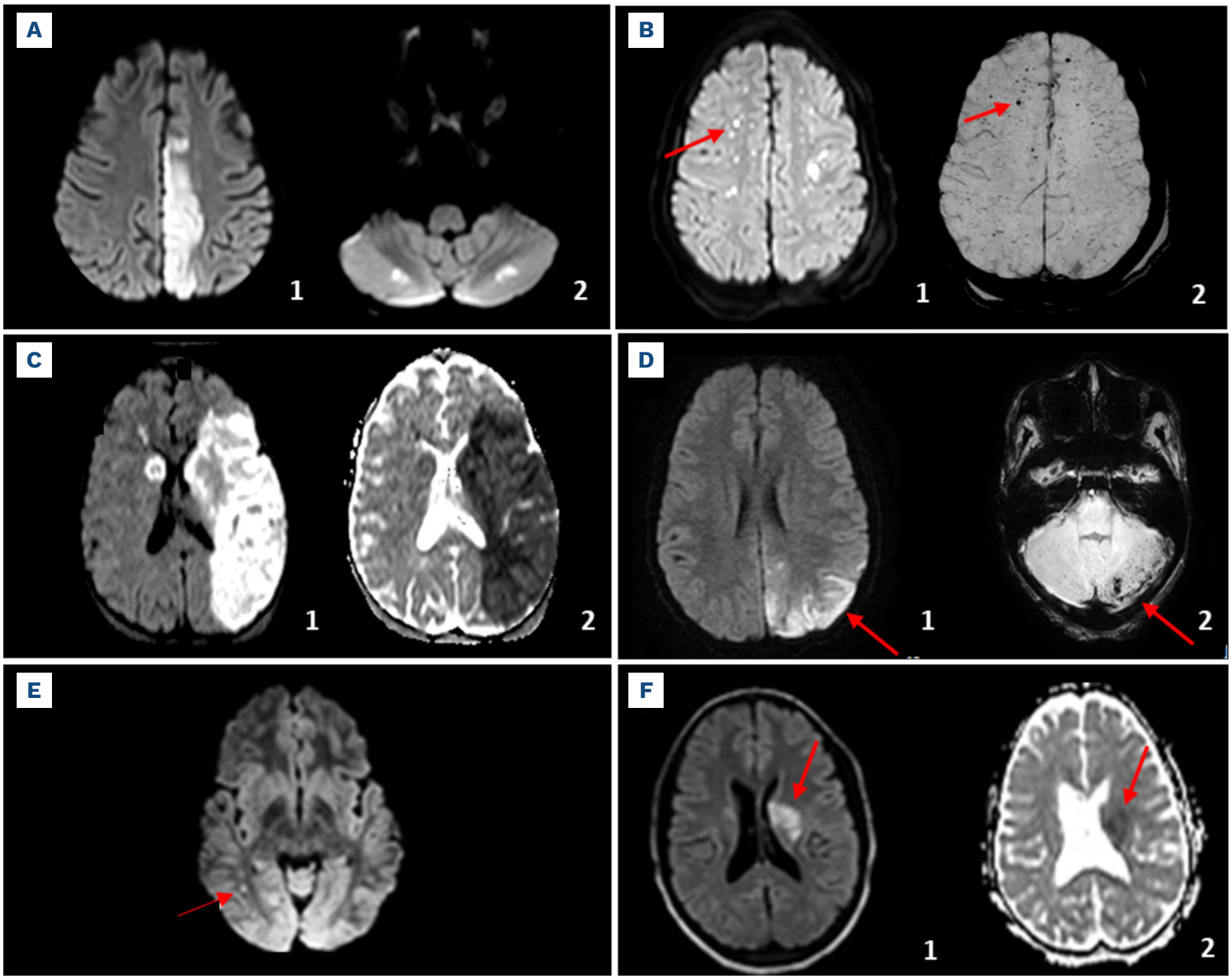

Figure 1. Representative brain magnetic resonance images of ischemic stroke of various etiologies in children with sickle cell disease with no sickle-related cerebral arteriopathy. (A) Reversible cerebral vasoconstriction syndrome (patient 1). (A1) Axial supratentorial view in diffusion weighted imaging (DWI) sequence showing a left medial parietal-occipital lesion. (A2) Axial infratentorial DWI view showing focal lesions in both cerebellar lobes. (B) Cerebral fat embolism syndrome (patient 10). (B1) Axial DWI view. (B2) Axial susceptibility weighted imaging (SWI) sequence: bilateral multiple punctiform ischemic and hemorrhagic lesions in the subcortical region and deep white matter (red arrows). (C) Arterial thrombosis (patient 3). (C1) Axial DWI view. (C2) Axial view of apparent diffusion coefficient map (ADC). Acute ischemic lesions in the complete territory of the left middle cerebral artery and in 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 (red arrow). (D2) Axial SWI, infratentorial view showing numerous petechiae predominating in the left cerebellar lobe (red arrow). (E) Low cerebral blood flow (patient 12). Axial DWI view: small foci of DWI hyperintensity in the right parietal-occipital white matter (red arrow). (F) Hyperviscosity (patient 8). (F1) Axial fluid attenuated inversion recovery (FLAIR) view. (F2) Axial ADC view. Ischemia in the left deep middle cerebral artery territory (red arrows).

patients had 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 following an episode of severe acute chest syndrome in the ICU. This last patient received corticosteroid therapy after two exchange transfusion sessions. He had a massive

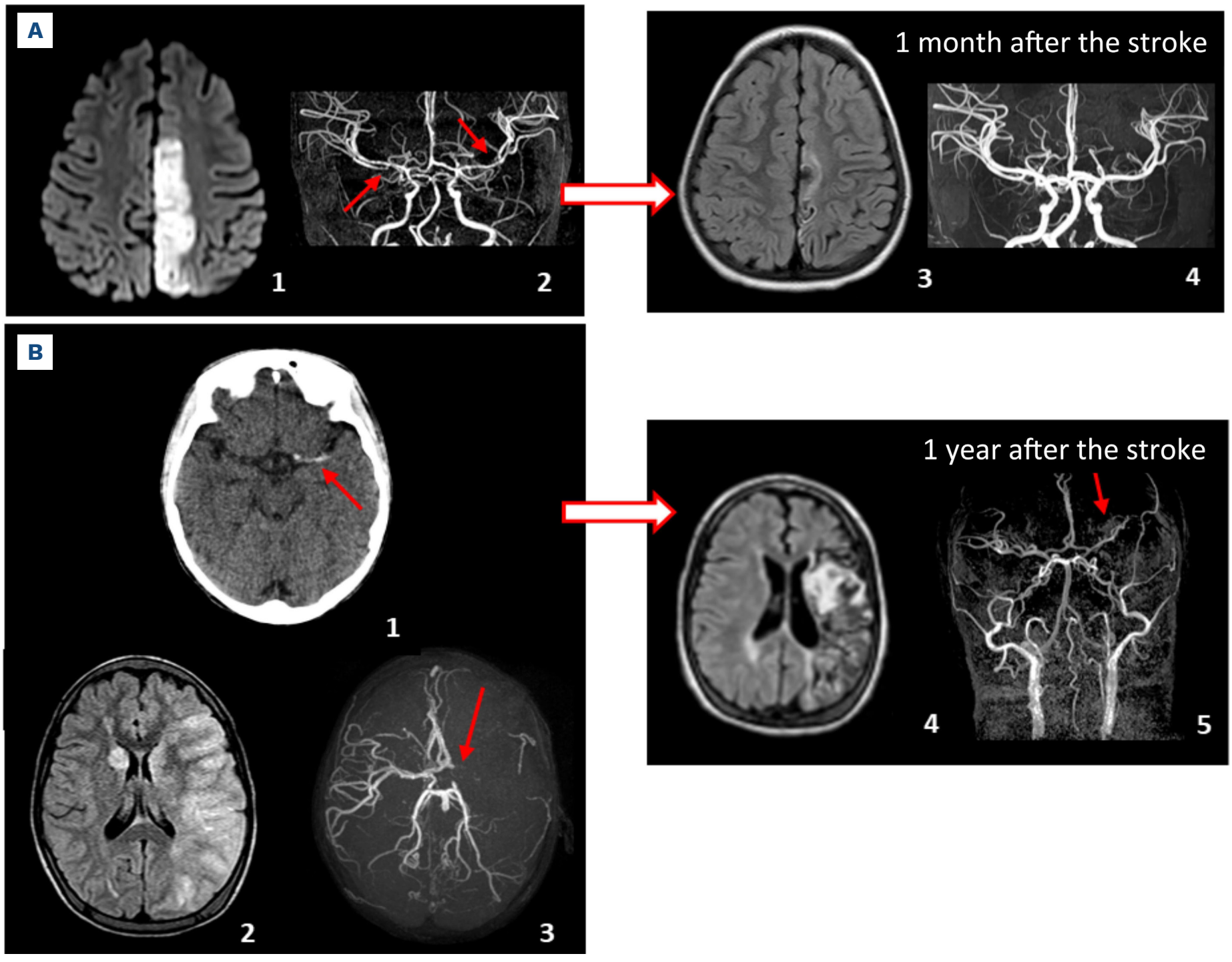

Figure 2. Course of ischemic stroke and vascular aspect on representative magnetic resonance images and magnetic resonance angiography in patients with no sickle-related arteriopathy. (A) Reversible cerebral vasoconstriction syndrome (patient 1). (A1) Magnetic resonance imaging (MRI) at the time of the stroke. Axial diffusion weighted imaging supratentorial view showing the left medial anterior cerebral artery territory infarct extending to the posterior cerebral artery territory. (A2) Three-dimensional time of flight (TOF) magnetic resonance angiography (MRA) shows multifocal segmental narrowing involving all cerebral arteries bilaterally (some are indicated with red arrows). (A3) MRI 1 month after the stroke. Axial fluid attenuated inversion recovery (FLAIR) view showing atrophic ischemic sequelae. (A4) MRA 1 month after the stroke shows normalization of arterial caliber. (B) Arterial thrombosis (patient 3). (B1) Head computed tomography without contrast in the acute phase of the stroke showing a large thrombus as spontaneous hyperdensity of the terminal left internal carotid artery and the left middle cerebral artery (red arrow). (B2) MRI at the time of the stroke. Axial FLAIR view showing an acute infarct in the complete left middle cerebral artery territory, the head of the right caudate nucleus and the right frontal deep white matter. (B3) On TOF MRA, absence of visualization of the internal carotid arteries, the first segment of the left anterior cerebral artery and left middle cerebral artery (red arrow). The basilar artery provides compensatory blood supply to 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, there is recovery of perfusion of the terminal segment of the left internal carotid artery and the proximal segment of the left middle cerebral artery and anterior cerebral artery. Collateral circulation pathways have developed from the external carotid arteries (red arrow).

posterior stroke 72 hours after beginning the corticosteroid therapy and died 2 days later.

One patient had a stroke in a context of infectious meningo-encephalitis 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 a painful vaso-occlusive crisis, 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 of iatrogenic origin.

Lastly, in two cases the main etiologic factor was considered to be blood hyperviscosity, based on a combination of clinical, laboratory and radiological features. Indeed, both patients had hemoglobin 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 48x10^9/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 a hemoglobin of 13.6 g/dL, 3 g higher than her baseline level. MRI revealed ischemia in the deep left middle cerebral artery 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 delayed hemolytic transfusion reaction, all patients received monthly exchange transfusions for at least 6 months after the acute phase.

Among the ten patients surviving 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 not to require exchange transfusions any longer as their MRA findings were 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 three remaining patients were still receiving monthly exchange transfusions due to corticosteroid-dependent nephrotic syndrome in one case, occurrence of stroke on hydroxyurea therapy with elevated hemoglobin with no other apparent contributing factors in one case, and appearance of SCD-related CA contralateral to the ischemic territory in the last case. Among the seven patients who stopped the transfusion program, four received, or continued to receive, treatment with hydroxyurea, the other three children had SC genotype.

Overall, the rate of neurological sequelae was similar in the two 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 among 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 re-

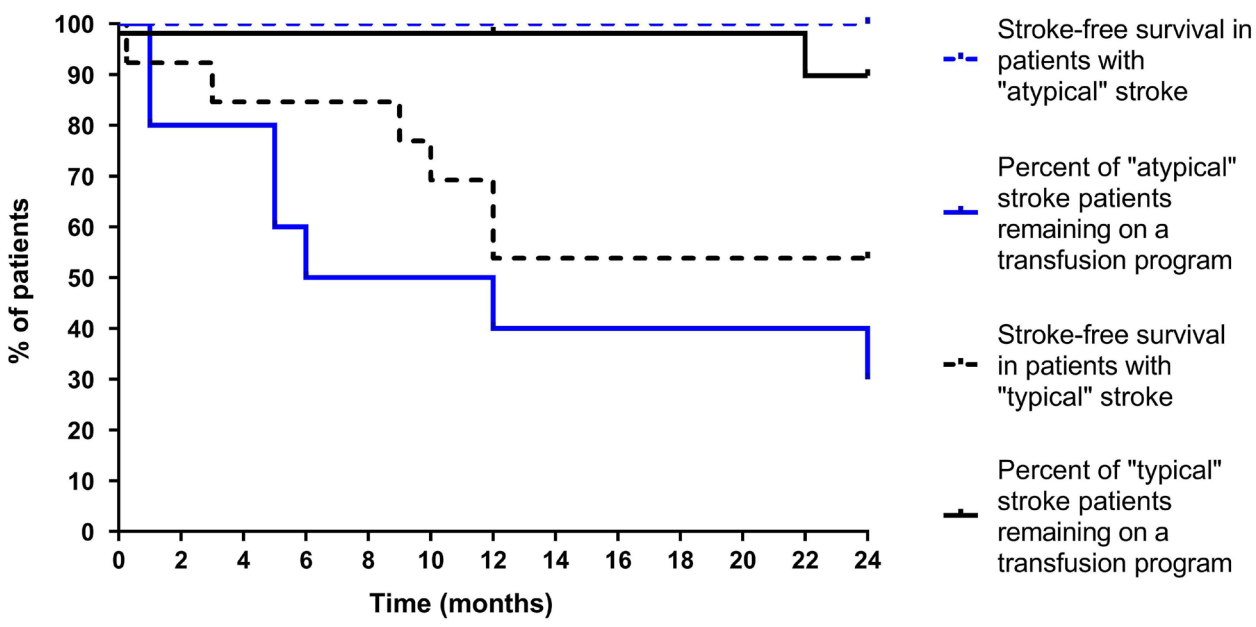

Figure 3. Post-stroke outcomes in patients with sickle cell disease. Follow-up for 24 months after stroke showing the duration of the exchange transfusion program and stroke recurrence in the two groups (patients with “typical” stroke and those with “atypical” stroke).

currence 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^0, 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 1,300 patients per year. 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.[12,18] 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, in whom 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 vaso-occlusive crises in the past 12 months and 28% had been treated 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 findings on the consequences 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 who were splenectomized before 3 years old.[19] This relation between splenic dysfunction and neurological complications in children should probably be investigated further.

Apart from those with cerebral arteriopathy, which children with sickle cell disease are at risk of stroke?

The first conclusion of our study is that stroke without CA can occur in children older than expected, at a median of 9 years of age and maximum of 15 years old in our study. As expected, patients with SCA had the highest risk of stroke,[3] 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 hospitalized in the ICU for another reason at stroke onset or had been in the preceding week. This suggests that acute complications related to SCD can aggravate baseline vascular instability, coagulation disorders, and precarious tissue oxygenation, thus promoting cerebral ischemia. Our results are consistent with published studies, including that by Kwiatkowski *et al.*,[14] who reported that 57% of ischemic strokes occur as part of a recent medical event in SCD children with a low risk of stroke. Particular clinical circumstances such as corticosteroid therapy, severe infections or severe pulmonary dysfunction 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.[20] Moreover, SCD is characterized by basal endothelial dysfunction related to chronic inflammation, which promotes long-term vascular wall thickening and, potentially, inappropriate vascular response.[13] 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).[21,22] Conversely, increased blood viscosity was suspected to be implicated in two cases of stroke in our study and has been reported as responsible for complications in SCD.[23,24] Given the underlying vascular dysfunction, the impaired microcirculation may be unable to compensate for a rapid increase in hemoglobin level by increasing vascular resistance and promoting red blood cell aggregation.[25] In addition, major hyperleukocytosis promoted by inflammation or corticosteroid therapy may increase blood viscosity.[26,27] Involvement of leukocytes, particularly neutrophils, in vascular and organ damage, including stroke, in SCD patients is well described above counts of 20 x10^9/L.[28] Inflammation could also promote increased adhesion of white blood cells to the endothelial wall, contributing to reduced blood flow and vascular damage.[29]

Necrosis of bone marrow in the long bones adds an embolic risk of another nature via the cerebral fat embolism syndrome. This 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.[30]

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 spontaneous reversibility in 1 to 3 months.

The best described predisposing factors are physical exercise, immersion in cold water, the Valsalva maneuver (forced expiration with a closed glottis) or vasoconstrictor treatment.[31] In SCD, several underlying risk factors may increase the risk of RCVS, such as blood viscosity fluctuations, disrupted regulation of vascular tone and endothelial dysfunction. Transfusion is also an identified risk factor in SCD children,[32,33] as are corticosteroids and immunomodulatory therapies. Lastly, exposure to cannabinoids, known to be a potential trigger,[34] should be considered in the case of RCVS in a 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 at risk of ischemic stroke.

What long-term treatment for sickle cell disease children with stroke without cerebral arteriopathy?

In accordance with guidelines,[35] 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 x10^9/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 hemoglobin 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 a transfusion program,[36] 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 an 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.[37,38] 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.

Disclosures

No conflicts of interest to disclose.

Contributions

SLL, SV and BK collected and analyzed the data. FM, LHV, VB, GI, and MB were in charge of the patients and reviewed the clinical and biological data. SV, AN, and MK reviewed the radiological data and prepared the figures. EL reviewed 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.

Data-sharing statement

Data are available on request to the corresponding author.

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