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CEREBROVASCULAR DISORDERS IN CHILDHOOD

Etiology, clinical presentation, and neuroimaging findings in a case series study

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ABSTRACT - *Objective:* To describe the main etiologies, neurological manifestations and neuro-imaging findings among children with sequelae of cerebrovascular disorders. *Method:* Case series study of children whose diagnosis was stroke sequelae. Variables studied were age at the time of first episode, number of episodes, etiology, motor deficits, epilepsy, and effected vascular territory. *Results:* Twenty three patients were studied. Average age at first episode was 6.91 (±2.08) years. Fourteen patients were female. The number of stroke events per patient ranged from one to five. The most frequent etiologies were heart disease and sickle cell anemia. The most frequent neurological deficit was right hemiparesis. Nine patients experienced seizures. The left middle cerebral artery was the most affected vascular area. *Conclusion:* Our findings are similar to those described in the literature. Despite a careful investigation, some causes of stroke remain unidentified.

KEY WORDS: stroke, childhood, etiology, clinical features, neuro-imaging.

Acidente vascular cerebral na infância: etiologia, apresentação clínica e achados de neuroimagem em um estudo de série de casos

RESUMO - *Objetivo:* Descrever as principais etiologias, manifestações neurológicas e achados de neuroimagem entre crianças com seqüela de acidente vascular cerebral (AVC). *Método:* Estudo de série de casos de crianças com seqüela de AVC isquêmico ou hemorrágico, analisando-se as variáveis: idade no primeiro episódio, número de eventos, etiologia, déficit motor, epilepsia e território vascular acometido. *Resultados:* Vinte e três pacientes foram incluídos, sendo 14 do sexo feminino. A idade do primeiro episódio foi 6.91 (±2,08) anos. O número de eventos por paciente variou entre 1 e 5. As etiologias mais freqüentes foram cardiopatia e anemia falciforme. O déficit mais encontrado foi a hemiparesia direita. Nove pacientes apresentaram convulsões. A artéria cerebral média esquerda foi o território vascular mais afetado. *Conclusão:* Os achados deste trabalho estão de acordo com a literatura em geral. Apesar de extensa investigação, alguns casos permanecem sem definição etiológica.

PALAVRAS-CHAVE: acidente vascular cerebral, infância, etiologia, manifestações clínicas, neuroimagem.

According to the World Health Organization, stroke is defined as rapidly developing clinical signs of focal disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin[1]. Stroke in childhood is a rare occurrence, with an estimated incidence of 13 in 100,000[1]. It frequently has the sequelae of cognitive and motor impairment, as well as epilepsy. In adults, stroke is often associated with the atherosclerotic process of the intracranial and cervical vessels; in childhood, it has various causes, such as thrombophilia (for example, protein C and S deficiencies), sickle cell anemia, infections, and acquired or congenital emboligenic heart diseases (for example, prosthetic heart valve and ventricular septal defects). However, the cause is often unidentified (cryptogenic stroke). The clinical presentation is often subtle and early radiological investigation may reveal normal findings. Outcomes include death in 6%, and neurological deficits in two thirds of the children[2].

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The objectives of the study are to describe the main etiologies and risk factors for ischemic or hemorrhagic stroke in children, and to describe the neurological manifestations (motor deficits and seizures), and neuro-imaging findings (affected vascular territory) in the sample.

METHOD

A case series study, with children aged between 2 months and 16 years by the time of the first stroke event, was conducted. All patients were admitted to our pediatric rehabilitation center (Rio de Janeiro, Brazil) between January 2002 and October 2004, with the main diagnosis of stroke sequelae. Variables studied were age at the first episode, number of episodes, etiology/risk factors, motor deficits, epilepsy/seizures, and affected vascular territory (according to the main cerebral arteries).

After a careful clinical history, physical and neurological examinations, laboratory tests, radiological (computerized tomography [CT] or magnetic resonance imaging [MRI] and/or magnetic resonance angiography [MRA]), cardiovascular and cerebrovascular investigations (electrocardiogram, echocardiogram, and carotid and transcranial Doppler ultrasound) were undertaken by all patients. Assays were done for factor-V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T gene mutations. Levels of anticardiolipin antibodies immunoglobulin G and M, homocysteine, protein C, protein S, antithrombin III, antinuclear antibodies, rheumatoid factor, serum complement, and lipoprotein A were measured. HIV infection (ELISA), syphilis (VDRL), sickle cell anemia (hemoglobin electrophoresis), and iron deficiency were also investigated. A metabolic screening was also done, and included: blood glucose, lactate and electrolytes levels, a lipid profile, and renal and liver function tests.

Table 1. Demographic and etiological profile of the sample.

Patients	Gender	Age*	Number of events**	Etiologies/risk factors
1	female	9 / 10	3	moyamoya/hyperhomocysteinemia
2	male	14 / 15	1	cryptogenic
3	female	2 / 10	1	heart disease (coarctation of aorta)
4	female	1 / 2	1	sickle cell anemia
5	female	15 / 15	1	cryptogenic
6	male	6 / 11	1	hyperhomocysteinemia
7	male	9 / 12	1	cryptogenic
8	female	15 / 15	1	heart disease (septal defect)
9	female	10 / 11	1	heart disease (prosthetic mitral valve)
10	female	1 / 14	1	heart disease (dilated cardiomyopathy)
11	male	1 / 6	1	hypoxemia and hypotension during an anesthetic procedure
12	male	13 / 13	1	traumatic internal carotid dissection
13	male	5 / 5	1	heart disease (septal defect)
14	male	4 / 5	1	cryptogenic
15	female	7 / 8	1	heart disease (acquired valve disease)
16	male	4 / 4	1	sickle cell anemia
17	female	7 / 11	3	sickle cell anemia
18	female	3 / 5	5	sickle cell anemia
19	female	13 / 13	1	rupture of a cortical AVM
20	male	1 / 1	1	sepsis with prolonged hypotension and intravascular disseminated coagulation
21	female	0.5/1	1	post-varicella
22	female	13/13	1	rupture of a cortical AVM
23	female	1/2	1	meningitis

AVM, arteriovenous malformation; *age (years) at the time of the first episode/ at admission; **number of clinically defined stroke events.

Cases of prenatal and neonatal stroke, and sinovenous thrombosis were excluded. All patients from whom typical radiological findings had not been identified were also excluded.

The SPSS software was used for statistical analysis. Chi-square test was done to analyze relationship between categorical variables. A *p* value less than 0.05 was considered statistically significant.

This study was approved by the Scientific and Ethics Committee of The Sarah Network of Hospitals for Rehabilitation and a signed informed consent was obtained from the parents.

RESULTS

Of the 27 patients with an initial diagnosis of stroke sequelae, four were excluded: three with intrauterine stroke and one with no compatible history and neuro-imaging findings. Median length of follow-up was 16 months (range 2-36 m). Age at admission varied between 1 and 15 years (average: 8.78±2.02 y). Age at first episode varied between 6 months and 15 years (average: 6.91±2.08 y). Fourteen patients were female. Only two patients had hemorrhagic stroke (patients 19 and 22 - Tables 1 and 2), both of them due to rupture of cortical arteriovenous malformation; all the others had ischemic events. The number of stroke events ranged from one to five (20 patients had experienced one episode).

During the follow-up period none of the children had a recurrent stroke. Some children received prophylactic treatments. However, this issue is beyond the scope of this study. The most frequent etiologies were heart disease (6 patients) and sickle cell anemia (4 patients). Four patients were classified as hav-

Table 2. Clinical presentation and affected vascular territory.

Patient	Motor deficits	Seizures	Vascular territory
1	quadriparesis	–	bilateral MCA and right ACA
2	right hemiparesis	–	left MCA
3	right hemiparesis	–	left VBC
4	left hemiparesis	–	bilateral MCA and right ACA
5	right hemiparesis	–	left MCA
6	right hemiplegia	+	left MCA
7	right hemiplegia	–	left MCA
8	right hemiplegia	–	left MCA
9	right hemiplegia	–	left MCA
10	right hemiplegia	–	left MCA
11	left hemiparesis	–	right MCA
12	right hemiplegia	–	left MCA
13	right hemiparesis and dystonia	+	left MCA
14	right hemiplegia	–	left VBC
15	right hemiparesis	–	left MCA
16	left hemiparesis	–	right MCA
17	quadriparesis	+	bilateral MCA
18	quadriparesis	+	bilateral MCA
19	right hemiparesis	+	left MCA
20	right hemiparesis	+	left MCA
21	right hemiparesis	+	left MCA
22	right hemiparesis	+	left MCA
23	none	+	left MCA

MCA, middle cerebral artery; ACA, anterior cerebral artery; VBC, vertebrobasilar circulation; –, absent; +, present.

Fig 1. Brain MRI T2 image of a 13-year-old female patient with moyamoya and recurrent ischemic stroke (arrows).

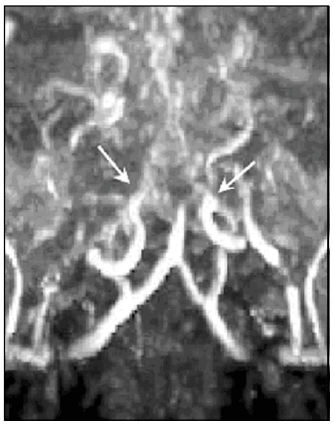

Fig 2. MRA of the same patient demonstrating the moyamoya "puff of smoke" appearance, and occlusion of both internal carotid arteries (arrows).

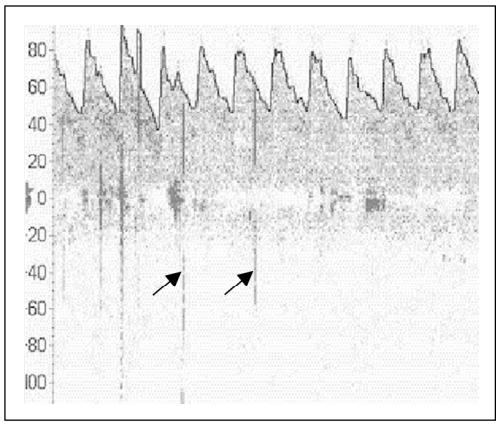

Fig 3. Left MCA in a transcranial Doppler sonogram of an 11–year-old girl with a prosthetic mitral valve showing high intensity transient signals (arrows) that indicates an embolic phenomenon.

ing a cryptogenic stroke. The most frequent motor deficit was right hemiparesis/hemiplegia (16 patients). Nine patients experienced seizures (4 of these only during the acute phase). The left middle cerebral artery (MCA) was the most common affected vascular area (19 cases). The number of vascular lesions per patient ranged from 1 to 7. Most of the patients had only one lesion. Cortical lesions were detected in 10 patients, while cortico-subcortical lesions were found in 6 patients. Subcortical infarcts of lacunar dimensions were found in 2 patients, and a pontine lacunar lesion was detected in 2 children. Only 3 patients had larger lesions in the lenticulostriate territory.

Regarding occurrence of seizures, neuro-imaging findings and number of events, some tendencies were found. The risk of developing seizures was not related to the number of events (p=0.40), however, it was strongly related to the presence of a cortical damage (p=0.01). The characteristics of the sample and clinical presentation are summarized in Tables 1 and 2, respectively.

Figures 1, 2 and 3 illustrate MRI, MRA and Doppler sonogram findings in the series.

DISCUSSION

As in many others case series reports, possible limitations of this are the absence of a control group, and the small size of the sample. It points to the need of prudence in interpretation of our results. However, some interesting comments could be drawn, as follows.

Although rare in childhood, stroke may have a considerable impact in daily live, in cognitive performance, and may be the first sign of an underlying systemic disease[1]. About half of the cases are ischemic, according to the literature[1]. We found only two patients with hemorrhagic stroke. One possible explanation is the higher mortality among patients with this condition during the acute phase. This study was conducted in a rehabilitation center, not in an emergency room. Regarding to gender, our results were similar to those found in Brazilian literature[3,4]. In general, in spite of the small sample, we found no statistically significant difference in gender distribution. Given our exclusion criteria, we did not study cases of neonatal stroke. As other studies included a wider age range, it was difficult to compare our findings regarding to age with theirs[3,4].

Congenital heart disease is one of the leading causes of stroke in children, accounting for 15-30%[1]. Heart disease is associated with a high risk of stroke, and can be congenital or acquired. Nearly half of strokes in children with heart disease are associated with cardiac procedures. On the other hand, untreated children are under a higher risk of an ischemic stroke[1,2]. Stroke is 250 times more frequent in children with sickle cell anemia[1]. Those with low hemoglobin, high white cell count, hypertension, chest pain crisis, and nocturnal hypoxemia are under a higher risk[1]. Some authors suggest that all patients with hemoglobin SS should be screened for internal carotid artery and MCA velocities using transcranial Doppler ultrasound[1,5], and it has been routinely done in our service. Those with values higher than 200 cm/s should be offered long term blood transfusion[5]. Infectious diseases, such as AIDS, varicella and meningitis are

very well recognized risk factors for stroke in childhood[1,6]. Many cases of stroke happen during (or some days after) an infectious disease. Probably, an inflammatory process of the intracranial vessels leads to their occlusion and, as a consequence, to the ischemic event[1]. Stroke can be the first manifestation of HIV-infection, so this diagnosis should be considered in all children with a focal neurological deficit[3,7]. Disorders of coagulation, mainly prothrombotic states, have been identified in from one third to one half of children with arterial ischemic stroke[1]. In neonates, anticardiolipin antibodies may be a risk factor for stroke, and in older children, deficiencies in proteins C and S have been reported[2,7]. Other risk factors/etiologies can also be involved: genetic predisposition, trauma, drugs, and metabolic and nutritional disorders[1,8,9]. It is important to note that many children may have multiple risk factors[1,10,11]. As reported in various studies, despite extensive evaluation for an underlying etiology, some cases of stroke in childhood may remain cryptogenic[1,2,12-14].

According to the literature, seizures are a common presentation of stroke in childhood, and cortical damage is a major risk factor for seizures development[1,3,4,12,15]. Among these patients, seizures are often controlled with a single antiepileptic drug[4]. We found 9 patients with seizures in our sample, but only 5 cases of definitive vascular epilepsy. All of these 9 patients had radiological signs of cortical involvement. All of our patients with vascular epilepsy had their seizures under control with a single drug.

Regarding the radiological findings, other studies also found a predominant involvement of the MCA among children with ischemic stroke[2,3]. Curiously, as in our sample, the left MCA was more frequently affected than the right one. As a consequence, right hemiparesis (or hemiplegia) is one of the most mentioned motor deficits among children with ischemic stroke sequelae[3,12,16].

The etiologies of stroke in childhood are diverse; those in this sample are similar to the ones described in the literature. Despite a careful investigation, some causes remain unidentified. Motor deficit and epilepsy (or a single seizure) are considerable consequences of stroke in childhood. There is also a wide range of neuro-imaging findings, however, the MCA is the most common affected vascular area.

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