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CEREBROVASCULAR DISEASE IN PEDIATRIC PATIENTS

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ABSTRACT - Although rare in childhood, stroke may have a serious impact when it happens in this stage of life. Also, it may be the first sign of a systemic disease. We report 12 cases of patients with stroke treated in the Neuropediatrics Unit of Hospital de Clínicas de Porto Alegre (HCPA) from March 1997 to March 2000. All patients, from term infants to 12-year-old children hospitalized in the Pediatrics Unit of HCPA, had clinical suspicion of stroke, which was later confirmed by radiological studies. Patient follow up ranged from 1 to 6 years (mean = 3.4 years). Presenting symptoms were hemiparesis in 9 patients, seizures in 7, deviation of labial commissure in 3, and loss of consciousness in 1. The increase in the number of cases of childhood stroke identified and later confirmed by noninvasive methods had helped in the determination of different ethiologies of stroke: the most frequent being hematologic, cardiac and genetic diseases. However, our study included 6 newborns with stroke whose ethiology was not identified. Seven children with seizures received phenobarbital. Six term infants had neonatal seizures secondary to stroke and restricted to the first 72 hours of life.

KEY WORDS: cerebrovascular disease, stroke, children.

Doença cerebrovascular em pacientes pediátricos

RESUMO - Doença cerebrovascular isquêmica (DCVI) é rara na infância, mas quando ocorre, o impacto pode ser muito sério. Pode ser a primeira manifestação de uma doença sistêmica. Relatamos a ocorrência de 12 casos de DCVI. Foram diagnosticados e tratados no Hospital de Clínicas de Porto Alegre (HCPA) na Unidade de Neuropediatria de março de 1997 a março de 2000. Todos os casos com suspeita clínica de DCVI foram confirmados por avaliação radiológica de recém-nascidos de termo (RNT) a crianças até 12 anos de idade, que internaram na Unidade de Pediatria do HCPA. Eles foram acompanhados de um a seis anos (média 3,4 anos). Os sintomas iniciais foram: hemiparesia em 9 pacientes, convulsões em 7, desvio da comissura labial em 3 e perda da consciência em um. O aumento do reconhecimento de DCVI em crianças, auxiliado pela confirmação do diagnóstico através de exames não invasivos, tem auxiliado na identificação da etiologia. As etiologias mais frequentes foram doenças hematológicas, cardíacas e genéticas. Contudo, nosso estudo mostrou 6 recém-nascidos com DCVI em que não foi identificada etiologia. Sete crianças com convulsões usaram fenobarbital. Em seis RNT com DCVI as convulsões estiveram restritas às primeiras 72 horas de vida.

PALAVRAS-CHAVE: doença cerebrovascular aguda, infância, AVC isquêmico.

Although rare in childhood, stroke may have a very serious impact and it may also be the first sign of systemic disease. Although its etiology may often be obscure, investigation must be as thorough as possible, not only to identify its cause, but also to estimate the risk of recurrence and to establish prognosis and adequate therapy[1]. The incidence of stroke in the pediatric population is of 2-3 cases per 100 000 children per year[2], which is 20 times lower than the incidence among 45- to 54-year-old adults.

Five factors should be considered in the pathophysiology of stroke in childhood: cerebral blood flow, endothelial factors, serum protein, platelets, and prostaglandins[3]. The most common predisposing factors are: cardiopathy[4], vasculitis[5], complications of cancer treatment[6], vascular thrombosis[7], and intracranial vascular malformations[7]. Other risk factors can also be involved in the onset of the disease: genetic predisposition, trauma, infection, and nutritional deficiencies[8-10].

Some of the genetic causes of CVD are homocystinuria, Fabry's disease, fibromuscular dysplasia, neurofibromatosis, protein C and S deficiency, Leiden's factor V and factor XII deficiency[7]. In spite of the

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long list of genetic factors that predispose to stroke in childhood, the full breadth of this interaction has not been accurately explained yet. There is a link between human leukocyte antigen B51 and stroke in childhood. Moyamoya disease seems to be linked to markers on chromosome 3p. Williams syndrome results from a mutation on chromosome 7q in the region that includes the elastin gene[7].

The HIV-infection diagnosis must be considered when focal neurologic symptoms are observed in the pediatric population[11,12], since stroke and seizures in childhood may be the first HIV-infection manifestation[13]. Necropsy investigations of HIV-infected children have revealed ischemic infarction of the thalamus, hypothalamus or internal capsule[13].

Sickle cell anemia is a strong risk factor for stroke secondary to the development of stenosis in the middle cerebral and internal carotid arteries[14]. Clinically and radiologically confirmed stenosis, associated with hematocrit < 20% and platelets < 500 000, is an independent risk factor for cognitive impairment[15]. Therefore, therapy should be started early to prevent neurological disabilities caused by stroke[4]. Hydroxyurea, a drug capable of decreasing the number of platelets and increasing hematocrit, has been used to prevent lesions[15,16].

The intelligence quotient (IQ) of children with disabilities caused by stroke is in the normal range, but is significantly lower than the IQ for the general population[17]. There is no evidence of gender differences in cognitive recovery. This study, however, does not discuss the lateralization of cerebral function and the application of different IQ scales[18]. Abnormal findings on conventional angiography or magnetic resonance imaging are observed for about 80% of children with stroke[14], but longitudinal studies have shown that 25-50% of the children with abnormal findings on initial cerebral angiography have normal angiograms at follow-up[19]. Several studies[20] have reported extremely favorable prognosis for stroke in term infants, and only one has reported focal seizures and apnea – also observed in other age groups[10] - restricted to the first three days of life[9].

Table 1. Clinical findings.

Presenting symptoms		N = 12	%
seizures		7	58
hemiparesis		9	75
deviation of labial commissure		3	25
loss of consciousness		1	8
affected hemibody	right	7	58
	left	5	42
Hospitalization time (mean ± SE)		10 ± 5 days	
Disability at discharge		6	50
Follow-up		9	75
Hemiparesis		8	66

SE, standard error.

Stroke is less frequent in children than in adults. However, the large number of possible etiologies suggests that this disease is underdiagnosed. Stroke in children may indicate the presence of concomitant diseases, such as sickle cell anemia and AIDS[2-6,13,15,16].

This study reports 12 cases of stroke in patients treated in the Neuropediatrics Unit of Hospital de Clínicas de Porto Alegre (HCPA) from March 1997 to March 2000.

METHOD

Patients with stroke were prospectively followed up at the outpatient service of the Neuropediatrics Unit of HCPA from March 1997 to March 2000. Inclusion criteria: children younger than 12 years of age, clinically suspected of stroke later confirmed by radiological studies, treated in the Pediatrics Unit of HCPA, and whose parents signed the informed consent document. Exclusion criteria: all patients for whom radiological findings had not confirmed stroke. We studied the following variables: race, sex, age at onset of symptoms and at the time of diagnosis, presence of neurological cognitive disability, concomitant disease, brain CT and EEG findings. IQ of patients under the age of 5 was measured with the WIPSI test. For 3 other patients, we used the WISC test[21]. The SPSS and Epi Info 6.04 software were used for statistical analyses.This study was approved by the Scientific and Ethics Committee of HCPA under the number 00.304.

RESULTS

Of the 12 patients with stroke, 11 were white and 7 were boys. Six were term newborns at the onset of symptoms. The others were 9 months to 6 years old when stroke occurred. Hemiparesis was observed in 9 patients, seizures in 7, deviation of labial commissure in 3, and loss of consciousness in one. The right hemibody was affected in 7 patients, and the left in 5. Mean hospitalization time was 10 days. Half of the patients showed some disability at hospital discharge (Table 1).

The middle cerebral artery territory was affected in all patients, and radiological signs of cerebral atrophy were found on brain CT of 4 patients. One newborn had cerebral atrophy; five patients underwent repeat brain CT at least one year after the stroke, and findings showed a reduction of the involved area; in 2 patients, diffuse cortical atrophy was observed in comparison with previous brain CT findings.

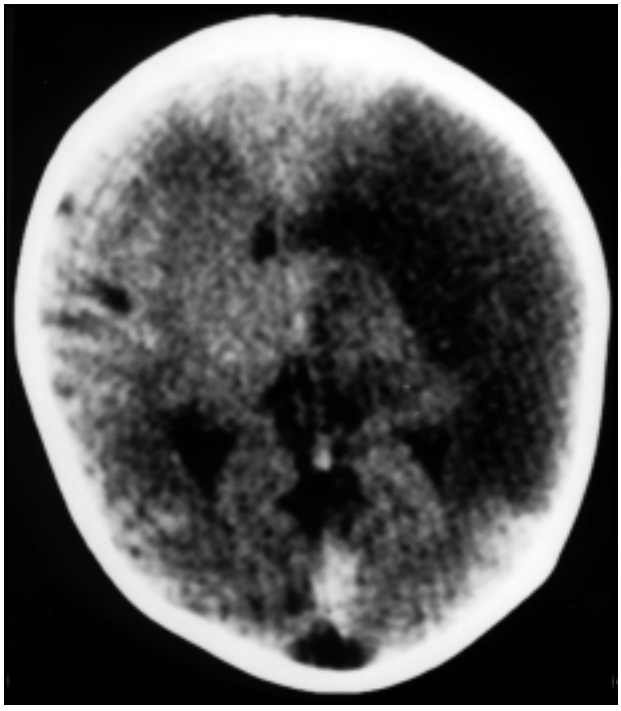

Fig 1. CT. Pacient 1 - Left midle cerebral artery territory involved.

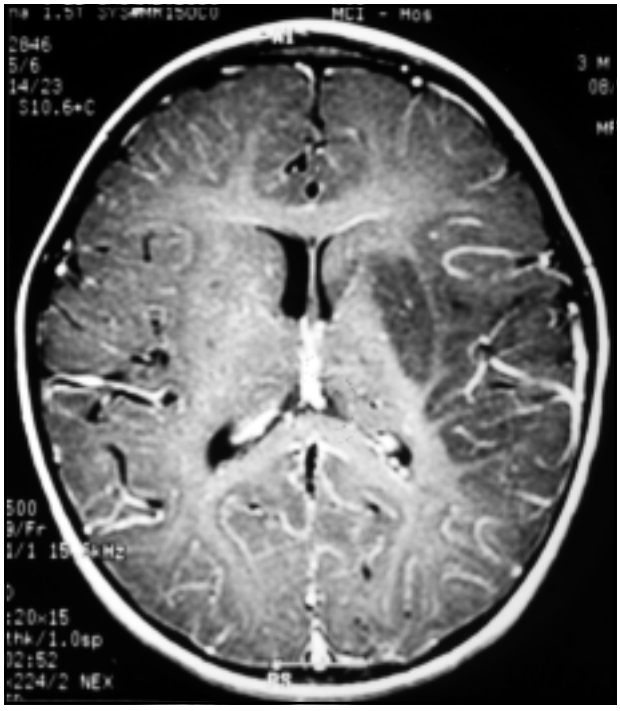

Fig 2. CT. Pacient 4 - Left midle cerebral artery territory involved.

Two patients showed concomitant hemiparesis and their IQ scores were lower (below 79) in both Performance and Verbal IQ tests (Figs 1, 2, and 3). There were no signs of cerebral atrophy on brain CT for the other 3 patients, who still had hemiparesis but whose IQ scores were normal.

EEG findings were recorded for all patients, and 10 showed a correlation with brain CT findings. Nine patients showed some type of disability at outpatient follow-up: the most frequent being hemiparesis (8 patients), with right side involvement in 7 patients (Table 1). Half of them had a concomitant disease that may have been the cause of stroke: congenital cardiopathy in 2 patients, sickle cell anemia in 1, AIDS in 1, acute lymphoblastic leukemia in 1, and deletion of long arm of chromosome 18 (18q - 21.3) in 1. Laboratory and radiological investigations, careful clinical history, and physical examination did not reveal any underlying etiology for the other six patients (all term newborns) (Table 2).

Patients were divided into two groups: patients with onset of symptoms in the neonatal period, and patients with onset at 9 months to 6 years of age. There were no statistical differences between the groups in relation to race, sex, signs of brain atrophy on CT, and correlation of EEG and CT findings. However, some significant differences were observed: at diagnosis, hemiparesis was present in 100% of the patients in the older children group and in 33% of the newborns ($p = .03$); concomitant disease was observed in 100% of the older children and absent in newborns ($p = .001$); predominance of damage to the right hemisphere was higher in older children ($p = .03$) (Table 3).

DISCUSSION

Cerebrovascular disease in children is less frequent than in adults, and it is underdiagnosed because physicians do not usually include it in differential diag-

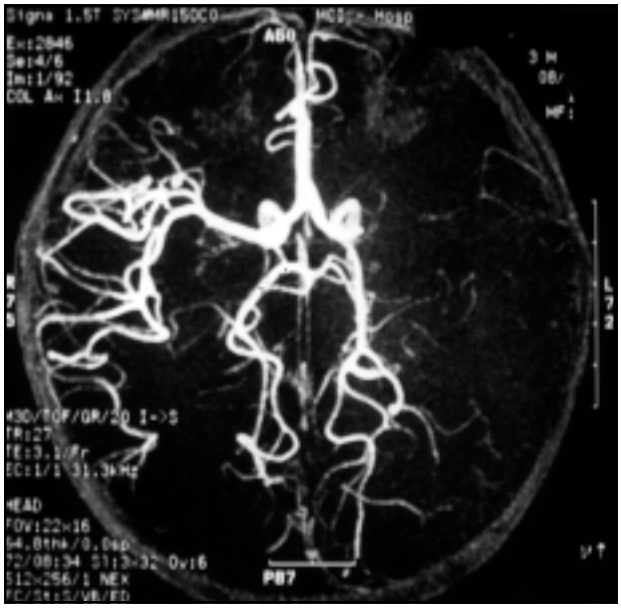

Fig 3. MRA. Pacient 7 - Left midle cerebral artery territory involved.

Table 2. Description of cases.

Patient	Race	Sex	Presenting symptoms	Age at on set	Concomitant disease	Disabilities
1	black	female	right hemiparesis	6 years	sickle cell anemia	right hemiparesis
2	white	male	right hemiparesis, left deviation of labial commissure and loss of consciousness	3 years	18 - 21.3	right hemiparesis
3	white	male	right focal seizures	48 hours	absent	right hemiparesis
4	white	male	left hemiparesis, right deviation of labial commissure	2 years	Tetralogy of Fallot	absent
5	white	male	seizures in right hemibody	24 hours	absent	right hemiparesis
6	white	male	right hemiparesis	48 hours	absent	right hemiparesis
7	white	female	right focal seizures	48 hours	absent	right hemiparesis
8	white	male	left hemiparesis	2 years	AIDS	absent
9	white	female	left hemiparesis and seizures	9 months	Noonan's syndrome	absent
10	white	male	left hemiparesis	6 years	ALL	left hemiparesis
11	white	female	right hemiparesis	48 hours	absent	right hemiparesis
12	white	female	seizures - right arm	48 hours	absent	right hemiparesis

ALL, acute lymphoblastic leukemia; AIDS, acquired immunodeficiency syndrome; 18-21.3, deletion of long arm of chromosome 18.

Table 3. Comparison between newborns and children older than 1 month.

Characteristics	Newborns		Older children		
	No.	%	No.	%	*p*
Total	6	100	6	100	NS
Race					
white	6	100	5	83	NS
black	0	0	1	17	
Sex					
female	3	50	2	33	NS
male	3	50	4	67	
Presenting symptoms					
seizures	4	66	3	50	NS
hemiparesis	2	33	6	100	.03*
Concomitant disease	0	0	6	100	.001*
Cortical atrophy	1	17	3	50	NS
Overlapping EEG and CT findings	5	83	5	83	NS
Hemiparesis					
right	6	100	2	33	.03*
left	0	0	4	67	

NS, not significant.

noses. Higher rates of identification of stroke in children, promoted by confirmation of diagnosis by noninvasive tests, have helped in the determination of etiology. Hematologic, cardiac and genetic diseases have been shown to be its most frequent causes. However, our study, similarly to others[17], has shown that etiology remains unknown in a significant number of children. Further research studies should be

conducted in an attempt to identify other etiologies[18,19,22].

Some studies have stressed the importance of suspecting stroke in HIV-infected patients when neurological focal signs are present[13,14]. We identified symptoms of hemiparesis in addition to episodes of focal seizures in one previously healthy patient, who had AIDS confirmed at etiologic investigation.

The incidence of seizures associated with stroke is high in childhood, mainly in the first two years of life, and seizures occur at the onset of disease in most cases. Cortical involvement is a risk factor for the development of seizures[23].

Of our 12 patients, 8 were administered the WIPSI test for children younger than 5 years, and 3 took the WISC test. Only 2 children had IQ scores below normal, which is in agreement with findings in the literature[21,24-26].

Our clinical findings for newborns are also in agreement with data in the literature[9,22,23]: most cases of stroke occur in term babies with a high Apgar score, who have seizures 24-48 hours after birth; and these patients respond better to the use of anticonvulsants. Our findings stress the importance of considering the hypothesis of stroke in newborns with seizures, even in the absence of hypoxic events. Multiple possible etiologies should be considered: sickle cell anemia, reported as the most common etiology; rare conditions, such as chromosomal anomalies; and even a first clinical sign of neuroAIDS in children[8,13].

Neuroimaging studies showed involvement of the middle cerebral artery in all patients, 66% on the left side. Cortical atrophy was found in 2 patients, exactly those who presented with cognitive impairment at outpatient follow-up. EEG changes were in agreement with radiological findings, as reported in literature[19,22,23].

Acute onset of focal signs with acute onset in children should always suggest stroke, and active investigation may reveal new causes to be added to the list of other better known etiologies[13,17,18].

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