

# STROKE SYNDROME IN CHILDREN

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## REZUMAT

Accidentele vasculare cerebrale (AVC) reprezintă o cauză importantă de morbiditate și mortalitate la adult, dar la copii ele sunt mult mai rare, incidența estimativă fiind de 2,5-2,7/100.000. AVC apar prin perturbarea circulației cerebrale ca urmare a unui proces de ischemie sau hemoragie cerebrală. În pediatrie, în aproximativ 45% din cazuri leziunile sunt de natură ischemică, și în mai mult de 50% din cazuri par a fi de cauză hemoragică. Etiologia AVC la copil variază de la cauze cardio-embolice, coagulopatii sau inflamații vasculare în AVC ischemice, la malformații arteriovenoase sau aneurisme cerebrale în cazul AVC hemoragice. Principala consecință a AVC ischemice sunt deficitul motor și cognitiv, precum și epilepsia, iar mortalitatea este 10%. Prognosticul AVC hemoragice depinde de cantitatea și localizarea acestora, precum și de starea de conștiență a pacientului în momentul hemoragiei. Mortalitatea după un episod hemoragic este de 20%, în timp ce mortalitatea după o intervenție chirurgicală este 0-13%. Incidența recidivelor este de aproximativ 13%. Cazurile pot evolua spre deficit motor, epilepsie, tulburări de comportament, dificultăți școlare.

**Cuvinte cheie:** accident vascular cerebral, ischemie cerebrală, hemoragie cerebrală, pediatrie

## ABSTRACT

Acute stroke syndromes (ASS) represent a major cause of morbidity and mortality in adults, but are rarer in children, with an estimated incidence of 2.5-2.7/100,000. They are produced by a perturbation of cerebral circulation as a result of ischemia or hemorrhage, and the lesions being ischemic in 45% of cases and hemorrhagic in more than 50% of cases in pediatric pathology. ASS have a complex etiology, ranging from cardio-embolic causes, disorders of coagulation or vascular inflammations, in case of ischemic strokes, to cerebral vascular abnormalities, arteriovenous malformations or cerebral aneurisms in case of hemorrhagic accidents. The most common consequences of ischemic strokes are motor, cognitive problems and epilepsy; the mortality being about 10%. The prognosis of hemorrhagic strokes depends on their quantity and localization as well as on the consciousness status of the patient during the onset of hemorrhage. The mean mortality after a hemorrhagic episode is 20%, whereas the mortality after the surgical intervention is 0-13%. The incidence of relapse is about 13%. The evolution goes towards motor deficiencies, epilepsy, behavioral modifications and school difficulties.

**Key Words:** acute stroke syndromes, cerebral vascular accidents, pediatrics

Acute stroke syndromes (ASS) are produced by a perturbation of cerebral circulation as a result of ischemia or hemorrhage, which persists more than 24 hours.<sup>1</sup> They represent a major cause of morbidity and mortality in adults with a predominance of ischemic accidents (80%), compared to hemorrhagic accidents (20%). ASS are more rare in children compared to adults, the incidence being estimated at 2.5-2.7/100,000 and lesions are likely to be ischemic in 45% of cases and hemorrhagic in more than 50% of cases.<sup>2</sup>

ASS in children have a complex etiology, with a preponderance of cardiovascular causes. Clinical features are different in children compared to those in adults: the onset is often milder, focalization signs are absent or less evident at the beginning, and neurological signs vary depending on the ischemic or hemorrhagic ASS.

## ISCHEMIC STROKE SYNDROME

Ischemic accidents occur as a result of arterial occlusion by an embolus or thrombus and the unilateral sensitive-motor deficiency represents actually the main reason of medical addressability of parents. However, symptoms vary from isolated motor deficiency (42%), migraine (38%) and seizures (36%), to cerebellum syndrome (6%), hemianopsia (6%) and inaugural coma (3%), diagnosis being confirmed by tomodensitometry and magnetic resonance imaging (MRI).<sup>3</sup>

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There are many causes of ischemic cerebral vascular accidents; however they can be classified in three main etiologic groups:

- cardio-embolic causes;
- disorders of coagulation;
- vascular inflammations.

The main causes of ischemic ASS are represented in Table 1.

**Table 1.** Causes of acute ischemic strokes in children

<b>CARDIAC DISEASES</b>	
▪	Congenital heart defects
▪	Cardiac arrhythmias
▪	Vascular abnormalities
▪	Endocarditis
<b>HEMATOLOGIC ABNORMALITIES</b>	
▪	Disseminated intravascular coagulation
▪	Protein C and protein S deficiency
▪	Factor V Leiden
▪	Antithrombin III deficiency
▪	Neoplasm
▪	Chemotherapy (L-asparaginase, methotrexate)
▪	Drepanocytosis
<b>VASCULAR CAUSES</b>	
▪	Moya Moya disease
▪	Fibromuscular dysplasia
▪	Takayasu arteritis
▪	Autoimmune diseases (systemic lupus erythematosus, polyarteritis nodosum)
▪	Metabolic diseases (homocystinuria, MELAS syndrome, Fabry disease)
▪	Infections
▪	Kawasaki disease
▪	Drug-induced inflammation (cocaine, amphetamine)
▪	Traumas

### Cardiac causes

Ischemic ASS have cardiac origin in 50% of cases.<sup>4</sup> Cerebral ischemia occurs as a result of an embolic process of cardiac nature, especially related with rheumatic valvular disease, mitral valve prolapse, cardiomyopathy, and during the evolution of endocarditis. On the other hand, ASS could represent a complication of cyanotic congenital heart defects. It is already known that 1.5-3.8% of severe cases of congenital heart defects can produce an ischemic cerebral accident.<sup>3</sup> The risk is very high for tetralogy of Fallot, transposition of the great vessels, tricuspid atresia and pulmonary atresia in particular.

### Hematological and vascular causes

Ischemic accidents may be caused by disorders of coagulation in children in 4% of cases.<sup>3</sup> Thromboembolic lesions occur as a result of a hypercoagulation

status, which appears in the case of constitutional deficiencies (C protein, S protein and antithrombin III), in the case of consume coagulopathy and also in syndromes with hyperproduction of antiphospholipid antibodies.<sup>5</sup> Drepanocytosis has complications such as ischemic accidents in 25% in homozygotes.<sup>6</sup> In addition, ischemia can follow a prethrombotic status associated with nephrotic syndrome, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, chemotherapy for neoplasm (especially L-asparaginase and methotrexate). It is already known that neoplasms represent an important cause of ASS in pediatrics. Therefore, approximately 4% of children with oncological diseases will suffer from ischemic cerebral lesions, considering the multiple physiopathological mechanisms involved, such as disseminated intravascular coagulation, as well as the chemotherapy and the radiotherapy, which accelerate the atherosclerosis processes.<sup>7</sup>

Moya Moya syndrome is an arterial disease responsible for the progressive occlusion of the distal part of internal carotid artery and Willis polygon. It is more frequent in children younger than 10 years with a second high incidence in adulthood.<sup>6</sup> Moya Moya syndrome is responsible for recurrent ischemic accidents in childhood and for hemorrhagic phenomena in adulthood.

Fibromuscular dysplasia is a diffuse arterial disease, which affects all vessels including carotids, reason for which it can be responsible for occlusive lesions.

Atherosclerosis constitutes the main cause of ischemic disturbances in adults and especially in old patients, being exceptional in children. However, cases of precocious atheromatosis processes can be seen in children with homocystinuria or with lipid disturbances, such as familial hypercholesterolemia, hypertriglyceridemia or HDL deficiency.<sup>3</sup>

### Neurocutaneous syndromes

Sturge-Weber disease or encephalotrigeminal angiomatosis is responsible for an ischemic chronic process, which affects the occipital cortex especially, whereas Recklinghausen neurofibromatosis is incriminated for the arterial dysplasia which produces cerebral infarcts.<sup>8</sup>

Autoimmune diseases such as systemic lupus erythematosus, polyarteritis nodosum, Wegener granulomatosis or Takayasu arteritis could represent a cause of ischemic stroke in children as well.

### Metabolic diseases associated with stroke

Vascular abnormalities can be seen in some metabolic diseases, for example homocystinuria, Fabry disease, ornithine transcarbamylase deficiency or mitochondrial disorders (MELAS and Leigh

syndrome). MELAS syndrome is a clinic entity which implies myopathy, encephalopathy, lactic acidosis and epilepsy as a consequence of recurrent ischemic episodes.<sup>9</sup>

Cerebral endarteritis or drug induced inflammation is seen in drug addict adolescents, but the onset could be during an infection. The most frequent etiologic agents are: herpetic virus, coxsackie virus, mycoplasma pneumoniae, rickettsia, brucella, salmonella typhi, HIV. During the infection phase, dehydration is an additive factor for ischemic phenomena.

#### **Traumatic causes**

They should be taken into consideration because they represent 22% of the causes of ischemic accidents through a process of arterial dissection.<sup>3</sup>

#### **Idiopathic etiology**

In approximately 20-50% of cases, etiology remains uncertain. Some studies suggest a genetic predisposition related to an immunologic marker HLA-B54 in children with idiopathic ischemic stroke.<sup>10,19</sup>

### **HEMORRHAGIC STROKES**

Intracranial hemorrhage varies, according to different authors, between 45% and 75% from the whole group of acute stroke syndromes in children. Their incidence has been estimated at 2.3/100,000 in children under 15 years old (Merrino Arribas and coworkers).<sup>11</sup>

Cerebral hemorrhages cause an increase of blood volume and intracranial pressure and accordingly, a decrease of cerebral perfusion. Clinical manifestations in hemorrhagic strokes are distinctive compared to ischemic strokes, migraine and consciousness disturbances being the most evident features. Giroud in his study has shown the following clinical findings: migraine (65%), sensitive motor deficiency (60%), aphasia (30%), inaugural coma (21%), seizures (39%), two thirds of the coma cases occurring in the first 24 hours.<sup>3</sup>

Intracranial hemorrhage affects cerebral hemispheres in 60% of cases, the cerebellum in 15% of cases, and the thalamus in 10% of patients.<sup>3</sup> The diagnosis is confirmed by CT and MRI.

The etiology is dominated by cerebral vascular abnormalities, arteriovenous malformations, and cerebral aneurisms in particular.

The principal causes of hemorrhagic strokes in children are presented in Table 2.

Arteriovenous malformations represent approximately 90% of cerebral vascular abnormalities in children. The most frequent situation is an incidental discovery during a cerebral hemorrhage. They are

**Table 2.** Causes of hemorrhagic strokes in children

▪ Arteriovenous malformations
▪ Cavernous angiomas
▪ Arterial aneurysm
▪ Leukemia (acute myeloid leukemia, M3-M5)
▪ Infections
▪ Idiopathic thrombocytopenic purpura
▪ Disorders of coagulation, hemophilia
▪ Drugs
▪ Hypertension

responsible for 30-50% of the hemorrhagic accidents in children, and their incidence has been estimated at 1/100,000.<sup>1,11</sup> The arteriovenous malformations are usually at the supratentorial level in only one hemisphere, rarely situated in the posterior fosse with a severe prognosis or they may be multiple malformations in 17% of cases. The risk for intracranial hemorrhage in arteriovenous malformations is 50-80%.<sup>11</sup>

Cavernous angiomas are rare malformations in children. The incidence is 0.4-0.7% in the general population with 2 peaks at 3 years old and at 11 years old.<sup>12</sup> Familial cases of such abnormalities have been described and the specific gene was shown to be on the long arm of chromosome 7. Cerebral angiomas are situated at the supratentorial level, rarely at the subtentorial or medullar level. They usually determine small and repetitive hemorrhages responsible for intracranial hypertension.

Cerebral arterial aneurisms in children are not rare, but manifest rarely or never, with a high incidence in children aged 2 to 10. Familial cases and predisposing factors have been described such as coarctation of the aorta, polycystic renal disease.<sup>3</sup> In 54-74% of cases, the hemorrhage is subarachnoidian with an important risk for relapsing (20-50% in the first week) and with a considerable rate of mortality (50% during the first month after the onset of the hemorrhage).

Cerebral hemorrhage during hypertension is rarer in children than in adults. The most common localizations for that are the putamen thalamus and cerebellum.<sup>1</sup>

Acute leukemia can lead to cerebral hemorrhage in children as it does in adults. Intracranial hemorrhage appears more often in the M3 and M5 phenotype of myeloid leukemia and is more likely to be in the parenchyma (1/5 of patients who died of acute leukemia had been found with hemorrhage in the parenchyma at necropsy).<sup>13</sup>

The incidence of cerebral hemorrhage in haemophilic patients has been estimated at 2.2-12.2% and is precipitated by cranial trauma. Drepanocytosis is responsible mainly for ischemic accidents. Thus, intracranial hemorrhage may be seen in idiopathic thrombocytopenic purpura 21 as well as in vitamin K deficiency, which complicates with hemorrhage in 63-65% of cases, most frequently at the subarachnoidian level.<sup>14</sup>

Primitive cerebral tumors, especially gliomas may produce cerebral hemorrhage, not only because of the disease, but also because of radiotherapy.

Drugs may cause hemorrhagic accidents through hypertension and vascular lesions. The risk for cerebral hemorrhage is 6.5 times greater in case of drug consumption.<sup>15</sup>

## PROGNOSIS OF STROKE SYNDROME IN CHILDREN

The data available about the outcome in children after strokes varies among studies due to differences in the duration of follow-up, functional measures, stroke type and population studied.<sup>9</sup>

In the case of ischemic strokes, combined data from several studies over the past 25 years revealed that on average, after an ischemic episode, 35% of children were neurologically normal, 55% developed cognitive or motor problems and 10% died by the outcome evaluation period. In addition to motor and cognitive problems, 29% developed recurrent seizures and 59% developed psychiatric disorders.<sup>9</sup> The recurrence rate ranged from 6% to 30% and most recurrences developed in the first 6 months.

The prognosis of hemorrhagic strokes depends on their quantity and localization as well as on the consciousness status of the patient at the moment of the onset of hemorrhage. Combined data showed that 38% of children were neurologically normal after a hemorrhagic episode, 41% had cognitive or motor abnormalities and 20% died by the outcome evaluation period.<sup>9</sup> In the cases with surgical intervention, the postoperative mortality was 0-13%.<sup>11</sup> The incidence of relapses was about 13%.<sup>3</sup>

In children, as in adults, subcortical strokes have been shown to have a better outcome than cortical strokes and Abram et al. found that predictors of poor outcome in Abram series included persistence of moderate to severe hemiparesis at 1 month, Moya-Moya and elevated triglycerides and LDL.

## CONCLUSIONS

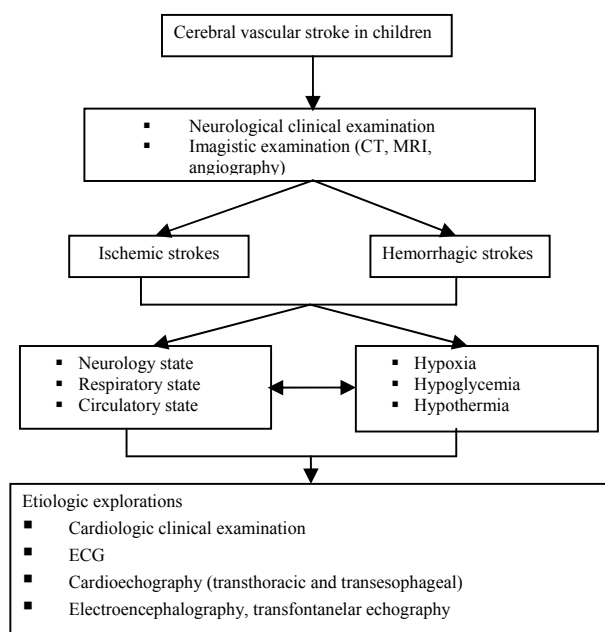
1. Although rare compared to adults, acute stroke syndrome in children can represent an important cause of mortality and chronic morbidity.

2. Clinically, the onset of ASS in children is often milder, focalization signs are absent or less evident, and neurological signs vary depending on the ischemic or hemorrhagic episode.

3. Etiologically, ischemic strokes are more often related to cardiac and embolic disorders, whereas hemorrhagic strokes are produced in children mainly because of cerebral malformations, while in adults hemorrhagic strokes are caused mostly by hypertension.

4. Prognostic, over half of children with stroke will develop lifelong cognitive or motor disability and up to one third will have a recurrent stroke.

5. An algorithm of diagnosis of acute stroke syndromes in children is presented in Figure 1.



**Figure 1.** Algorithm of diagnosis of acute stroke syndrome in children

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