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REVIEW ARTICLE

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Abstract:

Stroke in childhood is one of the most common causes of death or severe impairment worldwide, with annual incidence estimated from 1,3 to 13 cases/100.000 population. The definition of stroke consists both of arterial ischemic stroke (AIS) and hemorrhagic stroke. The incidence of ischemic and hemorrhagic stroke in children is approximately the same, in contrast to adults, while the incidence is higher in boys than it is in girls. Risks factors for pediatric stroke differ from those for adults, with arteriopathy and infections being the most commonly risk factors, followed by cardiac diseases. Clinical presentation of stroke in childhood depends on the affected area of the brain, with focal neurological deficit being the most common presentation in older children. The existence of stroke mimics and lack of typical findings in early neuroimaging lead to delay in diagnosis and poor prognosis. The adequate therapy has improved the outcome from pediatric stroke. However, this must be instituted within 3 to 6 hours. Prognosis of pediatric stroke is generally poor, depending on underlying condition. 10% of children who have stroke die, 20% have recurrent stroke and 70% have severe deficits. Our goal should be the rapid diagnosis and therapeutic management, which can contribute to improved outcomes in pediatric stroke.

Keywords: stroke, ischemia, hemorrhage, children

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Introduction-definitions

Stroke is a common cause of neurological disease in children and ranks in the top ten causes of death in USA, with poor outcome and neurological deficits for the survivors. More specifically, 10% of children who have a stroke die, 20% have further strike and 70% have seizures or other neurological deficits, such as motor deficits, communication disorders, cognitive and behavioral complications, hyperkinetic movement disorders, speech-language dysfunction, memory impairment and visual disorders [1].

The broad definition of pediatric stroke includes ischemic and hemorrhagic stroke. Ischemic stroke can be further subdivided into arterial ischemic stroke (AIS) and sinovenous thrombosis, whereas hemorrhagic stroke includes intracerebral and subarachnoid hemorrhage [1,2]. In childhood, 55% of stroke is ischemic and 45% hemorrhagic, whereas in adults 85% of stroke is ischemic [3].

Neonatal stroke encompasses both ischemic and hemorrhagic events resulting from disruption of either arteries or veins from early gestation through

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the first month of life. A special subtype of stroke is the "perinatal stroke", which describes cerebrovascular lesions that occur from 28 weeks' gestation through the first 7 days of life, although

some authors broaden this range from 20 weeks' gestation to 28 days after birth, and lesions occurring even before 20 weeks have been documented. Approximately 80% of these are ischemic and the remainders are due to cerebral venous sinus thrombosis (CVST) or hemorrhage. The perinatal stroke is distinguished from pediatric stroke because it has many differences concerning risk factors, clinical presentation and management [4].

According to the World Health Organization, "ischemic stroke" is a clinical syndrome of rapidly developing focal or global disturbance of brain function lasting more than 24 hours or leading to death, caused by arterial or venous infarction (thrombosis or embolism). In case that clinical symptoms last less than 24 hours, the condition is described with the term "transient ischemic stroke" [4]. "Hemorrhagic stroke" includes intracranial hemorrhage in the parenchyma of the brain or in the subarachnoid space. Patients with traumatic intracranial hemorrhage are excluded from the category of hemorrhagic stroke [4].

Epidemiological data

Population-based studies estimate the annual incidence of childhood stroke (ischemic and hemorrhagic) from 1,3 to 13 per 100.000 children. Only ischemic stroke affects 0,2 to 7,9 per 100.000 children, while among them 0,67 per 100.000 present with CVST [5,6]. Incidence of hemorrhagic stroke in children is estimated about 0,7-5,1/100.000, with most studies including also subarachnoid hemorrhage (with incidence 0,4 per 100.000 children) [2]. According to population-based studies estimating the epidemiology of stroke in children, the incidence of stroke seems to have increased over the last 25 years as a consequence of increase recognition, less invasive vascular diagnosis (MR/CT angiography) and therapeutic advances allowing children with predisposing conditions (congenital heart diseases, anemias, malignancy, meningitis) to survive [2,5,6,7,8].

Epidemiology of stroke in children differs from that in adults. In childhood, ischemic and hemorrhagic strokes have approximately the same incidence, in contrast to adults where hemorrhagic stroke is rarer and stands for only 20% of total strokes [2]. The incidence of stroke is lower in ages from 5 to 9 years

old, increases in puberty, and according to recent epidemiological studies the incidence is higher in boys than it is in girls (boys/girls: 1,49) [8,9,10]. Recent estimates suggest that in neonatal period stroke occurs in 1 per 4.000 live births, clearly a much higher rate than in older children, while neonatal stroke comprises 8-35% of total strokes [2]. The incidence of perinatal stroke is estimated from 20 to 60 per 100.000 live births. Arterial ischemic/hemorrhagic strokes in children usually concern anterior and middle cerebral arteries and their branches, as also thalamus and basal ganglia [1].

Clinical presentation of stroke

Approximately 50% of perinatal strokes will present acutely, usually as seizures, while the remainder present with focal deficits such as hemiparesis [11]. Older children usually present with hemiparesis, sensory disorders (hemianesthesia) and visual disturbance (hemianopia). Headache is usually present at hemorrhagic stroke, post-traumatic arterial thrombosis and venous thrombosis. Altered levels of consciousness indicates intracranial hemorrhage, ischemic infarction of middle cerebral artery or extensive infarct in posterior circulation. Seizures mainly occur in CVST, most frequently in neonatal period. Acute onset of clinical presentation usually indicates embolism or acute thrombosis due to post-traumatic rupture of arterial endothelium, while subacute onset of clinical presentation usually indicates progressive thrombosis [11,12]. Generally, clinical presentation of pediatric stroke is age-dependent. It is also varied and nonspecific, encompassing a broad differential diagnosis.

Risk factors for ischemic stroke

There are differences concerning risk factors for stroke between children and adults. In childhood, the predisposing conditions and risk factors for stroke include arteriopathies and infections, followed by heart diseases [13]. Table 1 shows with more details the risk factors for ischemic stroke. Approximately 70-90% of children presenting with ischemic stroke have at least one predisposing factor (symptomatic stroke), while a small proportion about 10-30% have no predisposing factors (cryptogenic stroke). Also, about 50% of children with stroke have no previous medical history [13,14].

TABLE I. Risk factors for ischemic stroke in childhood.

Cardiac Disorders (12%)	Hematologic disorders	Cerebral arteriopathy	Infections (23%)	Genetic disorders	Toxicity	Malignancy
Congenital cardiopathy	Sickle cell disease	Moyamoya disease	Chicken pox	Neurofibromatosis	L-Asparaginase	Leukemia
Endocarditis	Thrombophilia	Moyamoya syndrome	Infection with mycoplasma	Tuberous sclerosis	Radiation	Lymphoma
Cardiac valve disease	Iron deficiency anemia	Transient cerebral arteriopathy	Bacterial meningitis	Fabry disease		Cerebral tumors
Arrhythmia	Coagulation disorders	Arterial dissection	Infection with borrelia	Homocystinuria		
				Down syndrome		

At least 23% of pediatric ischemic strokes occur in the context of infection, and the importance of prior varicella infection as a risk factor for ischemic stroke has recently been recognized [1,13]. An association between varicella zoster virus and ischemic stroke in children has been suggested by the authors of several pediatric studies, including one case-control study that showed that children with stroke were 18 times more likely to have had chicken pox in the previous 9 months than healthy controls were. Secondary reactivation of varicella zoster virus is also associated with stroke. In a series of children with ischemic stroke, those with a history of varicella zoster virus infection were more likely to have basal ganglia infarcts, abnormal cerebrovascular imaging and recurrent ischemic stroke or transient ischemic attacks than those without. The probable mechanism of stroke in varicella zoster virus infection is arteriopathy as a result of invasion of the meninges by the viral pathogen, with secondary invasion of the virus and inflammatory cells into segments of the wall of the large cerebral arteries that are adjacent to the cerebrospinal fluid [13].

Dissection of the cervical and intracerebral arteries is an important cause of ischemic stroke in childhood that is diagnosed in up to 20% of cases in hospital series. In most cases the dissection has been associated with trauma or infection. However, connective tissue disorders such as Ehlers-Danlos

syndrome and Marfan syndrome can predispose to dissection.

Although cephalic and cervical pain are the most common presenting features of arterial dissection in adults, only half of pediatric patients report headache, while neck pain is rarely reported. So, the diagnosis is difficult and the most recommended method for diagnosis is angiography [13,15].

Moyamoya is a progressive bilateral or lateral stenosis of the internal carotid arteries and development of collateral blood flow. These collateral vessels give a “puff of smoke” appearance on angiography. Moyamoya can be either idiopathic, in which case it is referred to as “Moyamoya disease”, or secondary to underlying disorders, in which case it is referred to as “Moyamoya syndrome”. The underlying disorders include sickle cell disease, Down’s syndrome, and neurofibromatosis. Moyamoya in childhood usually presents with recurrent clinically overt ischemic events. However, seemingly asymptomatic Moyamoya syndrome can cause silent cerebral infarctions as well Moyamoya has been associated with about 6% of pediatric strokes [15].

Sickle cell disease is a major risk factor for overt and silent stroke in children, and 11% of patients with sickle cell disease have had a clinically overt stroke by the age of 20 years. In patients with sickle cell

disease, the incidence of ischemic stroke peaks between age of 2 and 5 years and that of hemorrhagic stroke between 20 and 30 years, which might represent a variable ability to generate collateral blood vessels to supply areas of ischemic brain. These vessels predispose the patient to hemorrhagic stroke because they tend to be fragile [16,17].

In the settings of deoxygenation acidosis or infection, sickle cell becomes denser, which causes the red blood cell to sickle. The sickled cells have increased adhesion to endothelium, which results in the formation of a thrombus. Sickle cell disease is associated with a progressive occlusive arteriopathy that involves the subarachnoid internal carotid arteries and proximal middle cerebral arteries, which is a risk factor for subsequent strokes despite transfusion therapy [17]. Risk factors for stroke in children with sickle cell disease that have been described include raised blood pressure, lower hemoglobin concentrations, high leukocyte count, previous transient ischemic attacks, priapism, acute anemia, recent acute chest syndrome, or transfusion within the past 2 weeks. However, chronic blood transfusion, resulting to targeted reduction of the sickle hemoglobin to <30% of the total hemoglobin, has decreased the risk for recurrent ischemic attacks up to 25-30% and also the risk for first ischemic event up to 92% [17].

The pathogenesis of CVST is multifactorial. Usually, the presence of CVST is due to a combination between prothrombotic disorders and underlying conditions. The incidence of CVST in children is estimated around 0,67 per 100.000, with most cases observed at first 3 months of life. The most frequently affected venous sinus is transverse and sigmoid [7]. Various risk factors for CVST have been described, such as dehydration (mainly in neonates), prothrombotic disorders, iron deficiency, sickle cell disease, uremic hemolytic syndrome, infections (meningitis, otitis media, sepsis), systemic lupus erythematosus, L-Asparaginase therapy, congenital cyanotic heart diseases, nephritic syndrome, inflammatory bowel disease. However, up to 25% of children with CVST have no underlying condition [18,19].

The clinical manifestations of CVST in children are at times nonspecific. At least 11,3% of children with CVST have no symptoms, while about 28,3 present

with increased intracranial pressure (headache, vomiting, papiledema) due to thrombosis of transverse venous sinus and mastoiditis. The combined presence of altered mental status, seizures and focal neurological deficit has been associated with thrombosis of sagittal (56%) and straight venous sinus [19].

Compared with ischemic stroke, outcome is generally better after CVST. Neurological deficits present in 43,4% of children with CVST. From these deficits about 24,5% are major and 18,8% minor. Major deficits have been associated with younger age, presentation of seizures, focal neurological signs, altered mental status and thrombosis of straight venous sinus [20].

Risk factors for perinatal stroke differ from previously reported risks factors and include cardiac disorders, coagulation disorders, trauma, infection, drugs, maternal and placental disorders, perinatal asphyxia, a history of infertility, chorioamnionitis, premature rupture of membranes, preeclampsia, and prothrombotic disorders [14].

Risk factors for hemorrhagic stroke

Risks factors for hemorrhagic stroke in childhood include arteriovenous malformations (AVMs), intracranial aneurisms, hemophilia, cerebral tumors and CVST [12,16,18]. Risks factors for hemorrhagic stroke are described in table 2.

The Diagnostic management and differential diagnosis of stroke

The differential diagnosis of stroke in children is broad, as numerous other conditions can present with acute neurologic deficits. In addition, the differential is further extended in young children because stroke may present with nonspecific signs such as seizures or lethargy. The differential diagnosis for acute hemiparesis in a child includes stroke, post-traumatic intracranial hematoma, tumors of central nervous system, encephalitis, demyelinating conditions (ADEM), complicated migraine, status epilepticus, metabolic stroke and prolonged postictal paresis (Todd's) [21].

Some metabolic conditions are associated with metabolic stroke rather than arterial stroke. This category includes the syndrome of mitochondrial encephalopathy with lactic acidosis and stroke like

TABLE II. Risk factors for hemorrhagic stroke in childhood.

Intracranial aneurism	<ul style="list-style-type: none"> - aortic isthmus stenosis - Polycystic kidneys (autosomal dominant) - Ehlers-Danlos syndrome type IV - Marfan syndrome
Arteriovenous malformations	
Hematologic disorders	<ul style="list-style-type: none"> - thrombocytopenia (<20.000 PLT) - sickle cell disease - congenital vitamin K deficiency - coagulation factors deficiency (VII, VIII, XIII,)
Cerebral tumors	
Cerebral venous sinus thrombosis	

TABLE III. Data from history and clinical examination helpful for diagnosis.

History	<ul style="list-style-type: none"> - head or neck injury (dissection of intracranial or outcranial vessel) - chicken pox or unexplained fever history (vasculitis) - tachycardia - progressive mental status impairment (Moyamoya disease, MELAS) - CVST symptoms (thrombophilia) - hemorrhagic rash, hemathrosis, abnormal bleeding or bruising - positive family history for thrombotic or hemorrhagic events
Clinical examination	<ul style="list-style-type: none"> - marfanoid phenotype (homocystinuria, vessel dissection) - skin anomalies: <ul style="list-style-type: none"> Angiokeratoma (Fabry disease) Xanthoma (hyperlipidemia) Café au lait spots (neurofibromatosis)

episodes (MELAS), organic acid disorders (methylamonic acidemia, propionic acidemia, isovaleric acidemia, glutaric aciduria types 1 and 2), ornithine transcarbamylase deficiency and carbohydrate deficient glycoprotein syndrome type Ia. MELAS is a maternally inherited multisystemic disorder caused by mutations of mitochondrial DNA. It is usually manifests in childhood after an early development. A relapsing-remitting course is most common, with stroke-like episodes leading to progressive neurologic dysfunction and dementia. The hallmark of this syndrome is the occurrence of stroke-like episodes that result in hemiparesis,

hemianopia or cortical blindness. Other common features include focal or generalized seizures, recurrent migraine-like headaches, vomiting, short stature, hearing loss and muscle weakness. Magnetic resonance imaging (MRI) classically shows signal change in both grey and white matter, predominantly in the occipital and parietal lobes, which mimic infraction (stroke-like lesions). However, their distribution does not follow vascular territories, and their pathophysiology is still controversial. In differential diagnosis, the following characteristics of stroke-like lesions presenting in MELAS will be helpful: preferential involvement of the cerebral

TABLE IV. Basic laboratory investigation for children with stroke

- brain MRI, intracranial vessels MRA (or CT angiography), MRV especially in cases when there is a suspicion for MELAS or homocystinuria
- outcranial vessels MRA, carotid arteries US or CT angiography
- EKG and heart US
- Full blood count
- Blood Fe, ferritin
- Hemoglobin electrophoresis
- Electrolytes, urea, creatinine, SGOT, SGPT
- Lipidemic profile
- Check for thrombophilia (table 6)
- ESR, CRP
- Antinuclear antibodies, antiphospholipid antibodies
- VDRL
- HIV
- metabolic screening: blood and urine aminogram, urine organic acids, galactic blood acid

In selected cases following tests will be helpful:

- Holter
- Neck x-ray (for relaxation or subluxation of atlantoaxial diarthrosis)
- Lumbar puncture (galactic acid measurement, possible infection)
- Cerebral vessels angiography

cortex, predilection to the posterior brain, reversible vasogenic edema and slowly progressive spread of the brain lesions. Thus, it is different from the pattern in ischemic stroke [21,22].

Generally, the clinical suspicion of Stroke in children should be present at following conditions: acute presentation of focal neurologic deficit, altered mental status especially combined with headache, seizures in mature neonates and seizures in children after heart operation. Computed tomography (CT) can diagnose large infarcts outside the hyper-acute frame and rule-out hemorrhage. MRI, particularly diffusion weighted studies, offer higher diagnostic sensitivity and specificity but unfortunately can't be used for emergency conditions in most medical

centers. The combination of MRI, MR angiography (MRA) and MR venography (MRV) can detect the cause of intracranial hemorrhage in 66% of cases. Angiography is considered to be a safe procedure [3,12]. Clinical examination and a detailed medical history are also necessary for a complete diagnosis. Table 3 includes data from clinical examination and history that are helpful to the diagnosis of pediatric stroke, while table 4 includes the essential laboratory tests.

The diagnosis of stroke in childhood is often delayed and is rarely made within 6 hours of symptom onset. Even when evaluated by a child neurologist, stroke is uncommonly considered or diagnosed at the first assessment. Probable reasons for this delay include lack of clinical suspicion of stroke in the young and the frequency of stroke mimics in children, including migraine, seizures, encephalitis and tumors. In a recent retrospective study of 209 children (aged 1 month to 18 years) who presented with acute arterial ischemic stroke, the diagnosis was 22,7 hours. In this particular study, the time from symptoms onset to hospital arrival was 1,7 hours but the time from presentation in hospital to diagnosis was 12,7 hours. In the end, only in 20% of children the diagnosis of stroke was made within 6 hours [23].

The diagnosis of hemorrhagic stroke in children can be made earlier compared to the diagnosis of ischemic stroke, because children with hemorrhagic stroke have a more acute symptom onset. Subarachnoid hemorrhage is characterized by severe headache, nuchal rigidity and progressive loss of consciousness, while intracerebral hemorrhage is characterized by focal neurologic signs and seizures [12,16].

Management of ischemic stroke

No randomized controlled trials of treatment in acute childhood stroke have been performed. In general, treatment of pediatric stroke is largely adapted from treatment of adult stroke. However, management of children with stroke diverges from that of adults with regard to the use of acute anticoagulation and the use of recombinant tissue plasminogen activator (t-PA). For all patients with suspected acute arterial ischemic stroke the following supportive measures are recommended: maintain airway-breathing-circulation (ABCs), maintain normoglycemia and normothermia, rapid and effective management of seizures, frequent

checks of mental status (for acute diagnosis of possible cerebral edema) and intussusceptions [14,24].

There are no randomized controlled trials examining the effectiveness of anticoagulation therapy for the treatment of ischemic stroke in children. Most clinicians agree on subcutaneous infusion of low molecular weight heparin (LMWH) 1mg/dose every 12 hours (for neonates 1,5 mg/kg/dose every 12 hours) for 6 to 7 days. In case intravenous unfractionated heparin is decided to be used, it is administrated initially in dose of 75 units/kg i.v. with total infusion duration >10 minutes. The initial infusion is followed by administration of 20 units/kg/hour for children older than 1 year old and 28 units/kg/hour for children younger than 1 year old. The goal of this treatment is the maintenance of APTT level from 60 to 85 seconds. Platelet's count number should be periodically checked due to the risk of thrombopenia as a result of therapy with heparin. This initial treatment is followed by administration of antithrombotic treatment per os with warfarin for 3 to 6 months. The initial dose is 0,2 mg/kg and the maintenance dose is 0,32 mg/kg for infants and 0,09 mg/kg for older children to achieve a goal of INR level of 2.0 to 3.0. Especially for children with artificial cardiac valve being on medication with warfarin, INR is recommended to reach the levels from 2.5 to 3.5 [14,25,26].

The administration of antiplatelet therapy, especially aspirin, is recommended by most clinicians as preservative measure for recurrence of stroke (initial dose in acute phase 3-5 mg/kg/day). For prolonged administration of aspirin the dose is 1-3 mg/kg/day. It is important to remember that the antiplatelet action of aspirin starts several days after the administration and aspirin should never replace the therapy with heparin when there is high risk of recurrent ischemic stroke or embolism [14,25].

Thrombolysis is approved for use in children older than 18 years of age, only when the treatment starts within 3 hours from symptoms onset, with i.v. administration of t-PA [14,27]. However, the effectiveness, safety and dose of t-PA for the treatment of pediatric ischemic stroke have not been established [25].

Neurosurgical procedures are recommended in patients with Moyamoya. However, not the whole medical community agrees concerning the best time for surgery. Some recommend the acute neurosurgical conduction even from the time of initial diagnosis, while others recommend the neurosurgical procedures only if initial medication fails to prevent the recurrence of strokes or if there is an evidence of low blood cerebral flow in neuroimaging with PET or SPECT. In case these findings are not present, aspirin is recommended for prevention in combination with maintenance of H₂O balance. Some researchers recommend the administration of Ca⁺⁺ channels antagonist but there is no good evidence to support this hypothesis [28].

In children with asymptomatic Moyamoya or mild symptoms is recommended an initial therapeutic approach with aspirin (2-5 mg/kg/day). In children with progressive and recurrent symptoms, due to insufficient cerebral blood flow or the presence of ischemic infarct, early surgery is recommended. It is proven that indirect procedures have better results for children than direct ones. Aspirin can be administrated for prevention before surgery or even in patients who are unable to have a surgery [25,29].

Management of hemorrhagic stroke

As previously described for management of ischemic stroke, the same supportive measures are also recommended for initial management of hemorrhagic stroke. Raise of body temperature higher than 37,5°C has been related to poor prognosis in adults, so it is generally recommended the administration of antifebrile treatment when the temperature raises (paracetamol). Administration of osmotic agents is recommended for management of perihemorrhagic edema. On the contrary, there is no evidence (from studies concerning adults) that cortisone is beneficial, while hyperglycemia as a result of cortisone's administration has been related to poor prognosis [14,30].

The administration of recombinant activated VIIa factor causes hemostasis has improved the acute prognosis in patients with intracerebral hemorrhage. The main restriction in use of this factor is the risk of thrombophilia and the need of acute administration of the factor (within 4 hours from hemorrhage onset)

which is extremely difficult in pediatric population, due to delayed diagnosis of stroke, as we previously documented [23,30].

Prognosis of pediatric stroke

More than half of children with stroke (about 70%) will have permanent neurologic deficit. Mortality in children due to stroke is 3,1 per 100.000 for ages younger than 2 year old, 0,4 per 100.000 for ages 1-4 years old and 0,2 per 100.000 for older children (5-14 years old) [31]. From the survivals, about 20% have recurrent episodes, 42% present with permanent neurological impairment (70% seizures) [1,32]. Recurrent episodes usually present within 5 years from first stroke. They mainly concern ischemic stroke, with higher risk within 3 weeks from the first stroke episode. Conditions that have been associated with higher risk of recurrent stroke are Moyamoya disease, arteriopathies, cardiac diseases, arterial dissection, sickle cell disease and thrombophilia [33,34].

Conclusions

Ischemic stroke is rare in childhood (0,6-7,9/100.000 children per year) and the presence of stroke has been associated with high mortality incidence, life quality impairment and severe disability. The acute administration of the adequate therapy (within 3-6 hours) has improved the prognosis of children after stroke. Unfortunately, the differential diagnosis of stroke is difficult due to a variety of mimic stroke conditions and there is an important delay in diagnosis of stroke in children.

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