Pediatric Ischemic Stroke: Acute Management and Areas of Research

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Stroke is defined as the rapid loss of brain function due to a decreased cerebral blood flow (CBF). It is a relatively rare disease in childhood, with an estimated incidence of 2.6-6.4/100 000/year[1-3] and serious long-term morbidity.[4] Ischemic stroke in children typically refers to arterial ischemic stroke (AIS). It is more frequent in the perinatal period (between 28 weeks of gestation to 28 days after birth) than in childhood (Figure 1; available at www.jpeds.com). The clinical presentation of AIS differs depending on age, involved artery, and cause. In newborns, seizures, apneas, hypotonia, episodes of duskiness, irritability, or poor feeding are common presenting symptoms. In children, frequently reported signs are focal neurologic deficits such as hemiplegia.[5] The vascular territory of the middle cerebral artery (MCA) is the most frequently affected.[6] We have primarily focused on pediatric stroke because neonatal stroke represents a different entity from a medical, epidemiologic, and pathophysiologic perspective.

Diagnosis

Diagnosis of acute stroke in children is still difficult, with a median time of 25 hours from clinical onset to radiologic confirmation.[7] Many cases remain misdiagnosed.[8] Perinatal stroke is usually associated with fetal or maternal comorbidities[9,10] (Table I). Pediatric AIS is associated to a variety of conditions[11,12] (Table II). Congenital heart disease and sickle-cell disease are the most common causes.[13] Moyamoya disease, arterial dissection,[14,15] and focal cerebral arteriopathy[16-18] are also frequently found.

Magnetic resonance imaging (MRI) and computed tomography (CT) angiography should be performed when children with acute neurologic deficits arrive at the emergency department if a thrombolytic or neurovascular intervention is suspected (ie, within the first hours from the onset of clinical signs). Non-contrast CT adequately excludes hemorrhagic stroke, and may reveal parenchymal hypodensity in arterial territories. However, CT is usually normal within the first 12 hours after the onset of symptoms.[6] MRI with diffusion-weighted imaging remains the most important imaging technique. Typical MRI findings in the acute phase include hyperintense signals in the white matter on T2-weighted images and fluid attenuation inverse recovery images, with a resultant loss of gray matter–white matter differentiation.[19] Fluid attenuation inverse recovery MRI sequences in children under the age of 2 years may not be helpful because of incomplete myelinization that complicates the correct interpretation of images.[20] The differentiation of the infarct core and the penumbra can be done by diffusion-weighted imaging plus perfusion imaging.[21] For children with suspected craniocervical arterial dissection, three-dimensional time-of-flight magnetic resonance angiography of the head and neck is recommended.[22]

AIS	Arterial ischemic stroke
ASA	Aspirin
BBB	Blood-brain barrier
CBF	Cerebral blood flow
CNS	Central nervous system
CT	Computed tomography
IAT	Intra-arterial thrombolysis
IVT	Intravenous thrombolysis
LMWH	Low molecular-weight heparin
MCA	Middle cerebral artery
MMPI	Matrix metalloproteinase inhibitors
MRI	Magnetic resonance imaging
MT	Mechanical thrombectomy
NVU	Neurovascular unit
SC	Stem cells
tPA	Tissue plasminogen activator
UFH	Unfractionated heparin

Physiology of AIS

From a cellular point of view, tissue infarction generates a complex sequence of events known as the ischemic cascade. When a vessel is occluded, the CBF is mostly reduced in the central region of the brain arterial territory (the infarct core), and centrifugally in a graded fashion (ischemic penumbra) due to residual perfusion from collateral blood vessels. If CBF is not restored within hours, the penumbral region becomes part of the core and cannot be rescued. The first damage in AIS is at the endothelial level, with increased permeability of the blood-brain barrier (BBB)[23,24] within the neurovascular unit (NVU).[25] The decreased CBF in the occluded vessel is responsible for the generation of free radicals, inflammation, spreading depression, and activation of glutamate receptors (excitotoxicity) within the NVU, causing vasogenic edema and brain damage.[26,27] The activation of matrix metalloproteinases and cyclooxygenase causes degradation of components of the basal lamina of the endothelium, inflammation and necrosis. Excess reactive oxygen species generation and Ca2+ dysregulation cause prolonged

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Table I. Perinatal and pediatric stroke subtypes

Subtypes of stroke	Age of diagnosis	Associated disorders
Perinatal stroke	Fetal: before birth by fetal imaging or neuropathologic examination	Maternal conditions: thrombotic disorders, infertility treatment, pre-eclampsia, premature and prolonged rupture of membranes, maternal autoimmune condition and autoantibody, antiphospholipid syndrome, chorioamnionitis
	Neonatal: after birth and before the 28th postnatal day	
	Presumed perinatal: after the 28th postnatal day but the ischemic event occurred supposedly, but not certainly, between 20th fetal week and the 28th postnatal day	Fetal/neonatal disorders: intrapartum asphyxia, mutations in procollagen IVa1, inherited thrombophilia, twin-to-twin transfusion syndrome, cardiac disorders, polycythemia, neonatal hypoglycemia, intrauterine growth restriction, infections, trauma, persistent fetal circulation and extracorporeal membrane oxygenation therapy
Childhood stroke	From the 28th postnatal day till the adult age	Structural anomalies of the cerebrovascular system and cerebral arteriopathy, systemic vascular disease, vasculitis, congenital and acquired heart disease, postinfectious vasculitis, hematologic disorders and coagulopathies, genetic, toxic, or metabolic causes, trauma

contraction of pericytes, which hinders the passage of blood cells and promotes their aggregation while decreasing plasma flow.[28] Apoptosis is triggered by inflammation, excitotoxicity, and oxidative stress, and is mediated by proteases of the caspase family.[29] Apoptosis is prominent in the ischemic penumbra.[30] A delayed restoration of CBF after transient ischemia aggravates apoptosis by restoring cellular energy processes (reperfusion injury).[31]

Acute Stroke Therapy

The main goal of pediatric stroke care is to protect the developing brain by minimizing acute brain injury. It is reasonable to start from adult AIS guidelines of American College of Chest Physicians, Royal College of Physicians, and the American Heart Association, to approach pediatric patients because of the lack of data from pediatric studies[32-36] (Table III).

To improve outcome, recanalization strategies (thrombolysis and thrombectomy) must be provided within the first few hours from onset of symptoms.[37,38] If AIS is diagnosed later, anticoagulants or antiplatelet agents are prescribed.

Intravenous Thrombolysis

Despite the absence of safety and efficacy data for children,[39] intravenous thrombolysis (IVT) by tissue plasminogen activator (tPA) is increasingly used in pediatric AIS.[40] A dose of 0.9 mg/kg of tPA (maximum 90 mg) is usually administrated, with 10% of the dose as a bolus over the first minute and the remaining dose as a 1-hour infusion.[41,42]

Intra-Arterial Thrombolysis

Extending the window of treatment with endovascular treatments up to 6 hours from symptom onset has been considered in adults.[43-47] The Prolyse in Acute Cerebral Thromboembolism II study and the MCA Embolism Local Fibrinolytic Intervention Trial reported a favorable outcome in 40% to 49% after intra-arterial thrombolysis (IAT) for ischemic stroke due to MCA occlusion.[48,49]

No randomized controlled trials have investigated whether IAT is also beneficial in children with AIS. Comparison with the results of Prolyse in Acute Cerebral Thrombo-Embolism II and MCA Embolism Local Fibrinolytic Intervention Trial is not feasible because of the low number of reported children

Table II. Common risk factors for pediatric AIS

Risk factor category	Etiology
Artheriopaties	
Structural anomalies of the cerebrovascular system	Arterial fibromuscular dysplasia, arteriovenous malformation, intracranial aneurysm, hereditary hemorrhagic telangiectasia, Sturge–Weber syndrome
Cerebral arteriopathy	Moyamoya disease, transient cerebral arteriopathy of childhood, primary central nervous system vasculitis, cranial radiotherapy
Vascular diseases	
Systemic	Volume depletion or systemic hypotension,systemic infection,superior vena cava syndrome, diabetes
Vasculitis	Meningitis, postinfectious systemic lupus erythematosus, polyarteritis nodosa, granulomatous angiitis, Takayasu's arteritis, rheumatoid arthritis, dermatomyositis, inflammatory bowel disease, hemolytic-uremic syndrome, drug abuse (cocaine, amphetamines)
Heart diseases	
Congenital	Ventricular/atrial septal defect, patent ductus arteriosus, aortic/mitral stenosis, coarctation, complex congenital heart defects
Acquired	Rheumatic heart disease, prosthetic heart valve, endocarditis, myocarditis, atrial myxoma, arrhythmia
Hematologic disorders and coagulopathies	Hemoglobinopathies, immune thrombocytopenic purpura, thrombotic thrombocytopenic, purpura, thrombocytosis, polycythemia, disseminated intravascular coagulation, leukemia or other neoplasms, congenital coagulation defects, oral contraceptive use, liver dysfunction with coagulation defect, vitamin K deficiency, Lupus anticoagulant, anticardiolipin antibodies
Genetic	
Syndromes	NF1, Down's syndrome, tuberous sclerosis, PHACES syndrome, connective tissue disorders, fibromuscular dysplasia
Metabolic disorders	Metabolic organicacidurias, homocysteinemia, mitochondrial disorders, Melas syndrome, lysosomal disorders, Fabry's disease
Traumatic	Child abuse,fat or air embolism, foreign body embolism, post-traumatic arterial dissection, blunt cervical arterial trauma, arteriography, post-traumatic carotid cavernous fistula, penetrating intracranial trauma