Stroke in children: Clinical Presentation and workup

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Stroke is characterized by the sudden loss of circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Stroke is a nonspecific term encompassing a heterogeneous group of pathophysiologic causes, including thrombosis, embolism, and hemorrhage. The incidence is 2.52 per 100,000 in the pediatric age group, that is approximately $\frac{1}{2}$ the incidence of brain tumours. Strokes currently are classified as either hemorrhagic or ischemic. Acute ischemic stroke refers to strokes caused by thrombosis or embolism and accounts for 50-60% of all strokes in children (Hutchison. Semin Pediatr Neurol 2004;11:139).

In the past, almost nothing could be done to help patients with acute stroke. Only in the past 25 years have significant advances been made in stroke prevention, supportive care, and rehabilitation. Still, little treatment existed for ischemic stroke until 1995, when recombinant tissue-type plasminogen activator (rt-PA) benefited some carefully selected patients with acute ischemic stroke (Carlsson et al. Neurology 2001;10:157). Many medical professionals now consider acute ischemic stroke to be a medical emergency which, when detected and treated early, can have few, if any, permanent sequelae.

On the macroscopic level, ischemic strokes most often are caused by extracranial embolism or intracranial thrombosis. On the cellular level, any process that disrupts blood flow to a portion of the brain unleashes an ischemic cascade, leading to the death of neurons and cerebral infarction. Understanding this chain of events is important for understanding current therapeutic approaches.

**Embolism**

Emboli may arise from the heart, the extracranial arteries or, rarely, the right-sided circulation (paradoxical emboli). The sources of cardiogenic emboli include valvular thrombi (eg, inmitral stenosis, endocarditis, prosthetic valves); dilated cardiomyopathy); and atrial myxomas. Lacunar infarcts account for 13-20% of all cerebral infarctions and usually involve the small terminal vasculature of the subcortical cerebrum and brainstem.

**Thrombosis**

The most common sites of thrombotic occlusion are cerebral artery branch points, especially in the distribution of the internal carotid artery. Arterial stenosis (ie, turbulent blood flow), atherosclerosis (ie, ulcerated plaques), and platelet adherence cause the formation of blood clots that either embolize or occlude the artery. Less common causes of thrombosis include polycythemia, protein C deficiency, fibromuscular dysplasia of the cerebral arteries, and prolonged vasoconstriction from migraine headache disorders. Any process that causes dissection of the cerebral arteries also can cause thrombotic stroke (eg, trauma, thoracic aortic dissection, arteritis). Occasionally, hypoperfusion distal to a stenotic or occluded artery or hypoperfusion of a vulnerable watershed region between 2 cerebral arterial territories can cause ischemic stroke (Lynch et al Prothrombotic factors in children with stroke or porencephaly. Pediatrics 2005;Aug).
Ischemic cascade

Within seconds to minutes of the loss of perfusion to a portion of the brain, an ischemic cascade is started that, if left unchecked, causes a central area of irreversible infarction surrounded by an area of potentially reversible ischemic penumbra. On the cellular level, the ischemic neuron becomes depolarized as ATP is depleted and membrane ion-transport systems fail. The resulting influx of calcium leads to the release of a number of neurotransmitters, including large quantities of glutamate, which in turn activates N-methyl-D-aspartate (NMDA) and other excitatory receptors on other neurons. These neurons then become depolarized, causing further calcium influx, further glutamate release, and local amplification of the initial ischemic insult. This massive calcium influx also activates various degradative enzymes, leading to the destruction of the cell membrane and other essential neuronal structures.

Free radicals, arachidonic acid, and nitric oxide are generated by this process, leading to further neuronal damage. Within hours to days after a stroke, specific genes are activated, initiating programmed cell death. Formation of cytokines and other factors that in turn cause further inflammation and microcirculatory compromise. Ultimately, the ischemic penumbra is consumed by these progressive insults, coalescing with the infarcted core, often within hours of the onset of the stroke.

The central goal of therapy in acute ischemic stroke is to preserve the ischemic penumbra. This can be accomplished by limiting the severity of ischemic injury (ie, neuronal protection) or reducing the duration of ischemia (ie, restoring blood flow to the compromised area). The ischemic cascade offers many points at which such interventions could be attempted. Multiple strategies for blocking this cascade are currently under investigation. The timing of restoring cerebral blood flow appears to be a critical factor, since initial animal and human imaging studies suggest that reperfusion must occur within 3 hours for the ischemic penumbra to be saved. Time also may prove to be a key factor in neuronal protection. Although still being studied, neuroprotective agents, which block the earliest stages of the ischemic cascade (eg, calcium channel blockers, glutamate receptor antagonists), are expected to be effective only within the earliest window of time.

Four territories

Anterior cerebral artery occlusions primarily affect frontal lobe function, producing altered mental status, impaired judgment, contralateral lower extremity weakness and hypesthesia, and gait apraxia.

Middle cerebral artery (MCA) occlusions commonly produce contralateral hemiparesis, contralateral hypesthesia, ipsilateral hemianopsia (blindness in one half of the visual field), and gaze preference toward the side of the lesion. Agnosia is common, and receptive or expressive aphasia may result if the lesion occurs in the dominant hemisphere. Since the MCA supplies the upper extremity motor strip, weakness of the arm and face is usually worse than that of the lower limb.

Posterior cerebral artery occlusions affect vision and thought, producing homonymous hemianopsia, cortical blindness, visual agnosia, altered mental status, and impaired memory.
Vertebrobasilar artery occlusions are notoriously difficult to detect because they cause a wide variety of cranial nerve, cerebellar, and brainstem deficits. These include vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypesthesia, syncope, and ataxia. Loss of pain and temperature sensation occurs on the ipsilateral face and contralateral body. In contrast, anterior strokes produce findings on one side of the body only.

**Investigation – main causes**

- Cardiac diseases
- SLE
- Kawasaki
- Hemolytic-uremic syndrome
- Moya-moya
- Fibromuscular dysplasia
- Dissecting aneurysm
- Ehler-Danlos (type IV), defect collagen III
- Arterial hypertension
- Phospholipid syndrome
- Coagulopathies
- Dyslipoproteinemia
- CDG
- Infectious diseases
- Tumours
- Panarteritis nodosa
- Takayasu
- Henoch-Schönlein
- Vascular dysplasia
- NFI
- Williams syndrome
- Pseudoxantoma elasticum
- Marfan syndrome
- Fabry disease
- Haemoglobinopathies
- MELAS
- Homocysteinuria
- Fabry
- Lyme disease
- Migraine

**Moyamoya disease**

Moyamoya disease (MMD) is a progressive occlusive disease of the cerebral vasculature with particular involvement of the circle of Willis and the arteries that feed it. Moyamoya (ie, Japanese for "puff of smoke") characterizes the appearance on angiography of abnormal vascular collateral networks that develop adjacent to the stenotic vessels. The steno-occlusive areas are usually bilateral, but unilateral involvement does not exclude the diagnosis. The exact etiology of MMD is unknown. Mortality rates are approximately 5% in children. Death is usually from hemorrhage. About 50-60% of affected individuals experience a gradual deterioration of cognitive function, presumably from recurrent strokes. The disease may be hereditary and multifactorial. It may occur by itself in a previously healthy individual. However, many disease states have been reported in association with MMD including the following:

- Apert syndrome, Down syndrome, Marfan syndrome, tuberous sclerosis, Turner syndrome, von Recklinghausen disease, and Hirschsprung disease
- Aplastic anemia, Fanconi anemia, sickle cell anemia, spherocytosis and lupus anticoagulant
- Atherosclerotic disease, coarctation of the aorta and fibromuscular dysplasia
- Cranial trauma
- Radiation injury
- Tuberculous meningitis
Moyamoya disease (MMD) could be treated surgically with encephalo-duro-arterio synangiosis (EDAS). The acetazolamid (Diamox) test and clinical symptoms were the main criteria to perform this surgical procedure.

**Hypertensive encephalopathy**

Hypertensive emergency, also called hypertensive crisis, is severe hypertension with acute impairment of an organ system eg, central nervous system. In these conditions, the blood pressure (BP) should be lowered aggressively over minutes to hours. The most common cause of hypertensive encephalopathy is abrupt blood pressure elevation in the chronically hypertensive patient. Accelerated hypertension is associated with group 3 Keith-Wagener-Barker retinopathy, which is characterized by retinal hemorrhages and exudates on funduscopic examination. Malignant hypertension is associated with group 4 Keith-Wagener-Barker retinopathy, which is characterized by the presence of papilledema, heralding the neurologic impairment from an elevated intracranial pressure.

Hypertensive encephalopathy describes the transient migratory neurologic symptoms associated with the malignant hypertensive state in hypertensive emergency. The clinical symptoms usually are reversible with prompt initiation of therapy. In the evaluation of an encephalopathic patient, exclude systemic disorders and various cerebrovascular events that may present with a similar constellation of clinical findings.

**The presenting symptoms include:**

- Headaches (85%): Mild headache alone in association with elevated BP does not indicate a hypertensive crisis.
- New-onset blurred vision (60%)
- Weight loss (75%)
- Nausea and vomiting
- Weakness and fatigue (30%)
- Confusion and mental status changes

Conditions predisposing a patient to elevated blood pressure are, chronic renal parenchymal disease, acute glomerulonephritis, renovascular hypertension, withdrawal from hypertensive agents (eg, clonidine), encephalitis, meningitis, pheochromocytoma, head trauma, collagen vascular disease and vasculitis.

In patients without hypertension, cerebral autoregulation preserves a relatively constant cerebral blood flow at a range of mean arterial blood pressures of 60-90 mm Hg. In chronically hypertensive patients, autoregulation is altered and shifted upward to maintain a relatively constant cerebral blood flow at a higher mean arterial blood pressure range.

When initiating therapy, the baseline blood pressure must be considered to avoid excessive blood pressure lowering and prevent cerebral ischemia. Lowering the mean arterial pressure by 25% and the diastolic blood pressure to 100-110 mm Hg is usually safe. Acute monitoring in an intensive care unit with arterial blood pressure monitoring is required for adequate titration of pharmacologic agents and monitoring of end organ function.