

NEUROLOGY

STROKE IN CHILDREN

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Abstract: *Pediatric stroke is an acute cerebrovascular event that occurs in children after 28 days of life up to 18 years of age. Pediatric stroke results in significant morbidity and mortality. Ischemic stroke can be due to arterial ischemia or venous sinus thrombosis. Hemorrhagic stroke is either due to non-traumatic, intra-parenchymal hemorrhage or subarachnoid hemorrhage. In young children, the symptoms could be non-specific. Stroke like conditions are very common, hence neuroimaging is mandatory for all cases of suspected stroke. Clinical awareness and recognition is crucial for diagnosis to ensure prompt management for better outcome.*

Keywords: *Stroke, Children, Pediatric stroke.*

Childhood stroke is a rare, but serious, medical condition affecting children (age range, 29 days to 18 years), which is associated with high morbidity and mortality. The risk factors are multifactorial in pediatric population and different from adults. There remains an insufficient understanding of childhood stroke, hence in this review; the etiologies, clinical features and consensus-based treatment are discussed.

Stroke is defined by World Health Organization (WHO) as ‘a clinical syndrome consisting of rapidly developing clinical signs of focal (global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin.¹ Stroke occurring from 28 weeks of gestation to the first 28 postnatal days of life is broadly classified as perinatal stroke while stroke occurring after 28 postnatal days of life to 18 years of age is classified as childhood stroke.² Perinatal stroke presents either shortly after birth in the early neonatal period with focal seizures

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or encephalopathy and it is termed a ‘acute perinatal stroke’ or can be a delayed presentation with pathological early hand preference and focal seizures due to chronic infarcts and termed as presumed perinatal stroke.^{3,4,5,6} Pediatric ischemic stroke affects an estimated 1.0 to 2.0 in 100 000 children (non-neonates) annually in Western countries. Hemorrhagic stroke makes up about half of pediatric stroke, with an incidence of approximately 1 to 1.7 in 100000 per year.⁷

Childhood stroke syndrome - Classification and types

Stroke in children can be typed as given in Box 1. Conventionally, stroke could be either ischemic or hemorrhagic. Ischemic stroke could be either due a thrombotic or embolic phenomenon. Ischemic stroke can either involve arterial territory or venous territory. There is a difference in the etiological evaluation and also in the management of arterial ischemic stroke and cerebral sinus venous thrombosis (venous stroke) and hence it is better to use the specific terminologies in clinical practice for better clarity. The term hemorrhagic stroke is used to refer all non-traumatic intracranial hemorrhage in children, with the exception of neonatal intra-ventricular hemorrhage. Hemorrhagic stroke can be either non-traumatic intra-parenchymal hemorrhage or subarachnoid

Box 1. Childhood stroke – Types

1. Ischemic stroke vs hemorrhagic stroke
2. Arterial stroke vs venous stroke
3. Anterior circulation stroke vs posterior circulation stroke

Box 2. Stroke Mimics (Mnemonic – HEMI)

H: Hypoglycemia (and hyperglycemia)

E: Epilepsy

M: Multiple sclerosis (Metabolic/MELAS and Migraine- hemiplegic as well as vestibular)

I: Intracranial tumors or infections such as meningitis, encephalitis and abscesses

Table I. Differentiation of stroke and stroke like episodes

Character	Stroke	Stroke like episodes
Deficits corresponding to specific vascular territory	Usually present	Rare
Onset	Usually abrupt	Gradual
Neurological features	Negative neurological symptoms like paralysis, aphasia, visual loss	Positive neurological symptoms such as involuntary movements, aura, hemiballismus
Level of consciousness	Normal or impaired	More commonly impaired (toxic or metabolic encephalopathy)
Weakness	Severe	Usually mild
Trigger/Precipitating factor	Uncommon	Common (migraine, hypoglycemia, vestibulopathy and metabolic disorders)
Neuroimaging - CT/MRI of brain	Corresponds to a specific vascular territory	Do not correspond to specific vascular territory
Magnetic resonance angiography	Vascular obstruction	Usually normal

hemorrhage. Transient ischemic attacks (TIA) and stroke like episodes are not stroke and this is not included in the WHO definition of stroke. Focal neurological deficit less than 24 hours is termed as TIA. Focal neurological deficit caused by direct-vascular cause are included under stroke like episodes. Table I shows how to differentiate stroke from stroke like episodes and Box 2 and Table II shows causes of stroke like episodes.

Arterial ischemic stroke

An arterial ischemic stroke (AIS) occurs due to an infarct in a defined arterial territory either due to thrombotic or embolic phenomenon. It presents with consistent clinical symptoms and signs depending upon the territory involved. AIS is the most common mechanism in 53-85% cases.⁸

The recent International Pediatric Stroke Study (IPSS) has identified at least one risk factor in 89% and presence of two or more risk factors in 47% of ischemic strokes.^{8,9} There are numerous risk factors and etiologies associated with childhood AIS (Box 3).

The IPSS group classifies causes of AIS into the following categories: Cardiac disease, sickle cell disease related arteriopathy, arterial dissection, moyamoya arteriopathy, other arteriopathy and other causes.⁹ Greatest recurrence risk among pediatric stroke is for AIS and among them arteriopathy has the highest risk for

recurrence.¹⁰ Childhood AIS is markedly different from adult, in risk factors and presentations.¹¹

Cerebral arteriopathy: Stenotic cerebral arteriopathy is identified as the AIS etiology in 60-80% of previously healthy children and the course of this arteriopathy is a stronger predictor of recurrent events.¹¹ Moyamoya angiopathy and sickle cell disease related arteriopathy are the most frequent form of chronic intracranial arteriopathy in children.¹¹ There are increasing reports of mineralizing angiopathy of lenticulostriate vessels. Primary angiitis of the CNS is rare in children.¹¹

Focal cerebral arteriopathy: Thirty to forty percent of children with AIS arteriopathy have a unilateral focal cerebral arteriopathy (FCA) characterized by unique form of arterial insult with unilateral focal stenosis of the terminal carotid trifurcation and a characteristic monophasic course.

Childhood FCA is suspected to be an inflammatory vessel wall pathology triggered by infections, typically varicella. Recurrence occur for a great majority in the first 6 months after the index event and hence, aspirin 5mg/kg/day is recommended for at least 18-24 months with further stabilization /regression of arterial stenosis which helps in preventing future recurrence. Stroke rarely recurs when the progression of the stenosis stops.¹¹

Table II. Stroke like episodes - clues to differentiate it from stroke

Stroke like episodes	Distinction from stroke
Migraine Hemiplegic migraine for anterior circulation stroke Vestibular migraine for posterior circulation stroke	Classical migraine history with headache of recurrent episodic nature with or without aura, with family history of migraine and normal neuroimaging
Infections Encephalitis, brain abscess, tuberculous meningitis, neurocysticercosis, tuberculoma	Fever, gradual onset, meningismus CSF analysis and neuroimaging are useful
Demyelination ADEM/MOG encephalitis NMOS, MS	Gradual onset, multifocal symptoms, encephalopathy +/-, optic nerve and spinal cord involvement.
Epilepsy Todd paralysis	Predominant positive symptoms (history of jerking of limbs or abnormal movements of face or eyes). Even in Todd paralysis, a positive symptoms like jerking of limbs precedes paresis which is a negative symptom
Inborn errors of metabolism 1. Mitochondrial disorder –MELAS. 2. Urea cycle disorder - OTC deficiency. 3. Fatty acid oxidation (FAO) defect. 4. Organic academia: Methylmalonic acidemia.	Preexisting delays/regression, multisystem disease, failure to thrive frequently, abnormal biochemical profiles.
Hypoglycemia	Risk factors e.g. insulin therapy, related to meals and additional systemic symptoms like sweating, tremors, tachycardia,
Alternating hemiplegia of childhood	History of contralateral events, presence of choreo-athetosis / dystonia and recovery after awakening from sleep
Acute cerebellar ataxia for posterior circulation stroke	Sudden onset, bilaterally symmetric ataxia; post viral often. History of exanthematous illness preceding the neurological symptoms
Vestibulopathy for posterior circulation stroke	Predominant vertigo and tinnitus as symptoms. Absence of negative symptoms.
Intracranial space occupying lesion (e.g.brain tumor)	Gradual onset with headache as a prominent symptom and altered level of consciousness. Features of raised intracranial pressure present.

ADEM:Acute disseminated encephalomyelitis, MOG: Myelin oligodendrocyte glycoprotein, NOSD: Neuromyelitis optica spectrum disorder, MS: Multiple sclerosis, MELAS: Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes

Moyamoya angiopathy

Moyamoya angiopathy (MMA) is a chronic progressive cerebral arteriopathy which results in slowly progressive occlusion of bilateral terminal portion of the internal carotid artery and development of collateral anastomoses pathway at the base of the brain.¹²

Girls are more affected than boys; usually bilateral in children. Unilateral involvement is observed in 18% and it progresses to bilateral within 2 years of onset of disease. It is diagnosed by angiography. It can be primary or secondary. Primary is an idiopathic vasculopathy called as moyamoya disease. Secondary is associated with other

Box 3. Arterial ischemic stroke - Etiologies

Cardiac

- Congenital: Congenital cyanotic heart disease, congenital acyanotic heart disease, cardiomyopathy
- Acquired: Cardiomyopathy, rheumatic heart disease, infective endocarditis, cardiac catheterization, arrhythmia

Hematological

- Iron deficiency anemia
- Sick cell anemia
- Thrombophilia- Prothrombotic states

Cervico-cephalic arterial dissections

- Traumatic / non-traumatic (Suspect vessel wall defect in trivial trauma).
- Dissection of internal carotid artery results from blunt trauma to the vessel in the tonsillar fossa, commonly seen with pencil injury.
- Spontaneous dissection should be suspected in the setting of acute infections.

Cerebral arteriopathy

- Idiopathic focal cerebral arteriopathy/Transient cerebral arteriopathy
- Post varicella angiopathy
- Vasculitis including primary CNS vasculitis, systemic vasculitis, infective vasculitis
- Fibromuscular dysplasia
- Moyamoya disease
- Moyamoya syndrome
- Mineralizing angiopathy of lenticulostriate vessels

Genetic

- Metabolic causes: Fabry's disease, homocystinuria, mitochondrial disorders
- Arterial anomalies like in neurofibromatosis type 1, PHACE syndrome (Posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies (coarctation of aorta) and eye anomalies)

Idiopathic

causes (secondary to Down syndrome, sickle cell disease, Alagille syndrome, William syndrome, neurofibromatosis type 1, post cranial irradiation) known as moyamoya syndrome.^{12,13}

Mineralizing angiopathy of lenticulostriate arteries (MALS)

It is a distinct clinical entity presenting in children commonly aged 6 months to 2 years with basal ganglia stroke often precipitated by minor head trauma. They usually present with rapid onset hemiparesis and often have transient hemidystonia. The exact cause of this entity is not known although multiple theories exist. Most believe it is due to the excessive stretching of the arteries at the point of arterial tethering during minor trauma when the angle between middle cerebral artery and lenticulostriate arteries are believed to be acute during infancy.^{14,15} It is also thought to be due to persistent form of fetal mineralisation of lenticulostriate vessels.¹⁶

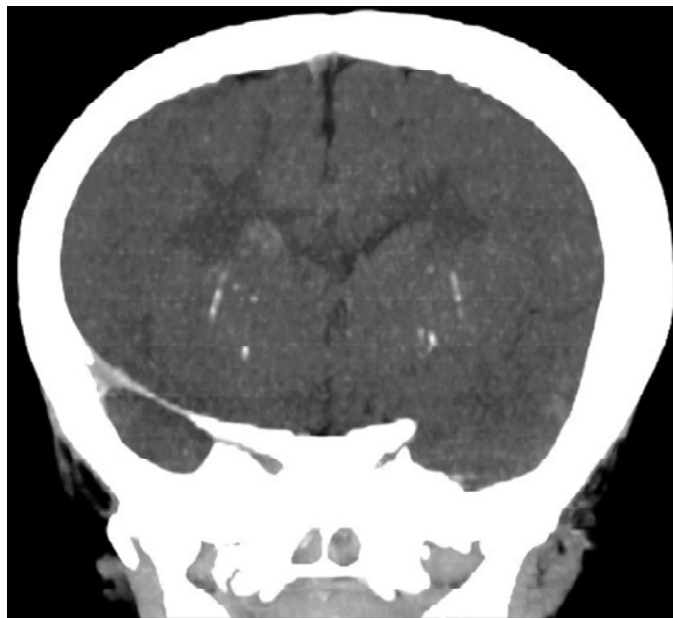


Fig.1. Coronal CT scan - Punctate microcalcifications in bilateral basal ganglia, in MALS.

It is important to note that MRI often fails to identify MALS and hence whenever gangliocapsular infarct is identified in the age of 6 months to 3 years, the advise is to do CT brain to delineate linear calcification in the lenticulostriate vessels (Fig.1). It is important for the clinician to be aware of this entity as the costly battery of etiological investigations could be avoided once there is clear cut evidence in the CT brain. Usually has a favorable prognosis with standard antithrombotic treatment like aspirin.¹⁴

Box 4. FAST

- Has the **FACE** drooped?
- Can they lift both **ARMS** and is there any drift of one side?
- Is the **SPEECH** slurred and do they understand you?
- **TIME** is critical and timely medical care

Box 5. Symptoms indicative of stroke where neuroimaging indicated

1. New onset focal seizures
2. New onset severe headache
3. Altered mental status including transient loss of consciousness or behavioral changes
4. New onset ataxia, vertigo or dizziness
5. Sudden onset of neck pain or neck stiffness
6. Witnessed acute focal neurological deficit which has since resolved¹¹

Clinical features

Hemiparesis or focal deficit, change in mental status, headache, seizure and speech disturbances are common.¹⁷ Use the FAST (Face, Arms, Speech, Time) criteria to determine stroke in children and young people, but do not rule out stroke in the absence of FAST signs.¹⁸ **‘FAST’** is an acronym useful in the screening and recognition of stroke at community level in western guidelines (Box.4).

Symptoms which are highly suggestive of stroke which warrant urgent neuroimaging are acute focal neurological deficit, aphasia and reduced level of consciousness (age-appropriate Glasgow Coma Scale (GCS) less-than 15 or AVPU (‘Alert, Voice, Pain, Unresponsive’) less than alert at presentation.¹⁸

Symptoms which may be indicative of stroke where neuroimaging has to be strongly considered is given in Box 5. Be aware that non-specific symptoms like nausea or vomiting, fever, can be present in a child presenting with stroke¹⁸. Younger the age, more non-specific is the presentation and suspecting diagnosis of stroke in young children is challenging. Anterior circulation strokes are

Table III. Clinical features and differences between anterior and posterior circulation stroke based on specific territory

Anterior circulation strokes (Middle cerebral artery territory - MCA territory stroke is the most common)		Posterior circulation strokes (Posterior cerebral artery territory, vertebra-basilar system and all brainstem stroke syndromes)
Anterior cerebral artery territory	Middle cerebral artery territory	Posterior cerebral artery territory
Clinical features: Hemiparesis, aphasia, visual field defects, altered mental status (Seizures, aphasia, apraxia, amnesia suggest cortical involvement)		Clinical features: Ataxia, vertigo, diplopia, vomiting
1. Weakness of lower limbs	Contralateral hemiplegia With or without	1. Sensory loss, pain, movement disorder due to thalamic involvement
2. Loss of voluntary control of micturition	1. Contralateral hemianaesthesia 2. Contralateral homonymous hemianopia 3. Aphasia 4. Apraxia	2. Visual field loss such as hemianopia or quadrantanopia 3. Cortical blindness
3. Behavioral and memory disturbances		

Table IV. Brainstem stroke syndromes (included under posterior circulation stroke)

Midbrain	Pons	Medulla
Weber syndrome Third cranial nerve (CN) palsy with contralateral hemiplegia	Foville syndrome Sixth and seventh CN palsy with contra lateral hemiplegia	Wallenburg syndrome Ipsilateral cerebellar signs, sensory loss over face, bulbar muscle weakness, nystagmus, vertigo (inferior vestibular nucleus) and Horner syndrome. Contralateral loss of pain and temperature over the torso and limbs. No or minimal cortico spinal fibers involvement as they are ventral in location
Benedikt syndrome Third CN palsy + contra lateral hemiplegia + tremor, rigidity & ataxia on opposite side	Milliard Gubler syndrome Seventh CN palsy + contra lateral hemiplegia	Dejerine syndrome Ipsilateral 12 th CN palsy with contralateral hemiplegia with contralateral loss of posterior column sensations
Parinaud syndrome Upward gaze palsy, pupillary light-near dissociation, convergence retraction nystagmus, lid retraction		

Table V. Investigations for arterial ischemic stroke (AIS)

First tier investigations	Second tier investigations (to be done within first week)	Third tier investigations (Performed on an individual basis)
CT brain with CT angiography	Lipid profile, serum lactate	Metabolic work up: ABG, serum lactate, serum ammonia, TMS, urinary GCMS
MRI brain with MRA + / - MRV		
CBC, peripheral smear and sickling test, ESR, blood glucose	Transcranial & carotid Doppler	Vasculitis work up
Renal and liver function test, urine routine, if needed screen for infections (retroviral serology, enteroviral studies, mycoplasma / Varicella zoster virus titers)	Prothrombotic work up: Serum homocysteine, factor V Leiden mutation, methylenetetrahydrofolate reductase (MTHFR) gene mutation, prothrombin gene mutation, lupus anticoagulant, APLA antibodies	Digital subtraction angiography
Coagulation profile: PT and aPTT	Prothrombotic work up (Tests which are to be done after 3 months): Protein C, protein S, anti-thrombin III, Activated Protein C resistance	Mitochondrial disorder work up: CSF lactate and pyruvate, muscle biopsy, genetic studies
Cardiac evaluation including ECG with prolonged lead II recording and Echocardiography		Leptomeningeal / brain biopsy in cases of suspected small vessel primary CNS vasculitis

more common than posterior circulation strokes. Table III and IV gives the clinical features and differences between anterior and posterior circulation strokes.

Investigations

Neuroimaging is mandatory in all cases in whom stroke is suspected. MRI brain is the investigation of choice in pediatric stroke. However, it is recommended that at least a computerized tomography (CT) brain with computerized tomographic angiography (CTA) is performed within one hour of arrival at hospital. CTA is limited to intracranial part if there is evidence of intracranial hemorrhage or from vertex to neck, if the CT brain does not show hemorrhage.¹⁸ The stepwise investigations to be done is listed in Table V.

CT brain

It is the initial imaging if hemorrhagic stroke is suspected. CT brain may be normal in first 12 hours in ischemic stroke. More than 50% of CT brain done at the time of presentation of the child with stroke is normal. CT brain is a good choice for pediatric stroke in an acute care setting where MRI brain facility is not available.^{17,18} It is also helpful in identifying mineralizing angiopathy of lenticulo striate arteries (MALS) by detecting calcifications.

MRI brain

MRI brain with MR angiography is the neuroimaging investigation of choice in a child with suspected stroke. It has the advantage of picking up infarcts earlier than CT brain. It is also better in detection of small size infarcts, multiple tiny infarcts, infarcts in posterior fossa, infarcts which underwent hemorrhagic transformation and in detection of flow voids compared to CT brain (Fig.2). MRI brain can also guide in estimating the timing of infarcts.

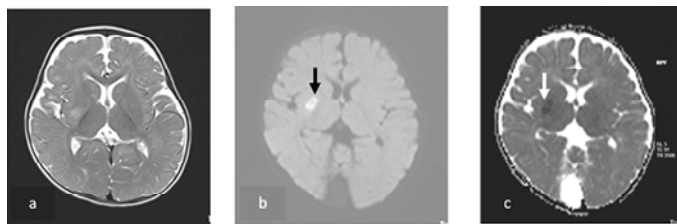


Fig. 2. Axial T2WI (a) Hyperintensity in right posterior putamen. DWI MR (b) and corresponding ADC mapping (c) Diffusion restriction in right posterior putamen in a child with mineralizing angiopathy of lenticulostriate arteries.

Role of MR angiography

MRA should be done for suspected cases of stroke at the time of undertaking MRI. This should cover the aortic arch to vertex in AIS and can be limited to the intracranial circulation in hemorrhagic stroke.¹⁸ Vessel anatomy and flow voids could be visualized clearly. MR angiography can confirm vascular occlusion and suggest possible arteriopathy if it involves large/medium vessels.¹⁷ (Remember MRA is often normal in small vessel vasculopathy and only a leptomeningeal / brain biopsy is diagnostic in that case).

Digital subtraction angiography (DSA)

DSA is the ideal investigation of choice which helps in the detection of vasculitis, collateral blood flow, emboli within blood vessels and aneurysmal anatomy. It is a useful investigation of choice in moyamoya disease where puff of smoke appearance is made out. Also consider DSA in any child where etiology of stroke has not been made out.¹⁷

Treatment

It should address both acute treatment as well as long term treatment (Table VI).

Acute phase

a. Supportive care

Stabilize airway, breathing and circulation. Temperature and oxygenation should be maintained normally along with avoidance of hypoglycemia as well as hyperglycemia. In an acute setting, relative hypertension is not rare but must not be aggressively lowered except in the following circumstances: (i) in children who are otherwise eligible for intravenous thrombolysis but in whom systolic blood pressure exceeds 95th percentile for age by more than 15% and (ii) hypertensive encephalopathy in the presence of end organ damage or dysfunction, e.g. cardiac or renal failure.

In case of stroke with features of raised intracranial pressure, measures to reduce cerebral edema is required to ensure adequate cerebral perfusion pressure. Swallowing should be assessed concurrently with sensorium to decide about mode of nutritional support (enteral - PO/tube, parenteral).

After stabilization, physiotherapy and rehabilitation should be planned. Early mobilization is needed to decrease the risk of aspiration pneumonia, pressure sores, deep vein thrombosis and contractures. Current evidence on supportive therapy for stroke in children is shown in Box.6.

Table VI. Treatment of arterial ischemic stroke (AIS)

Acute phase	Long term
1. Supportive care	1. Neurorehabilitation and seizure control in case of epilepsy
2. Anti-platelet therapy like aspirin	2. Secondary prevention <ul style="list-style-type: none"> • Anti-platelet drugs - Aspirin, clopidogrel, dipyridamole • Anti-coagulation therapy : LMWH / Warfarin
3. Anticoagulant therapy like heparin, low molecular weight heparin	3. Specific treatment of underlying cause
4. Recanalization therapy: Acute thrombolytic therapy and mechanical thrombectomy	

Box.6 Evidence regarding supportive therapy after stroke in children**Class I Recommendation**

Supportive measures for AIS should include control of fever, maintenance of normal oxygenation, control of systemic hypertension, and normalization of serum glucose levels. (Class I, Level of Evidence C)

Class II Recommendation

Treat dehydration and anemia in children with stroke. (Class IIa, Level of Evidence C)

Class III Recommendations

1. There is no evidence that the use of supplemental oxygen is beneficial in children with stroke in the absence of hypoxemia.
2. In the absence of clinical or electrographic seizures, prophylactic administration of antiepileptic medications in children with ischemic stroke is not necessary
3. In the absence of additional data confirming its safety and efficacy, hypothermia should not be used in children with stroke except in the context of a clinical trial.

a. Antiplatelet therapy- Antiplatelet agents like aspirin are recommended in children with ischemic cerebral infarction in the oral dose of 3-5 mg/kg /day. It has to be started within 48 hours after ischemic stroke unless anti coagulation / anti thrombolytic therapy is planned. Though there are no RCTs, it is an important drug to be given in arterial ischemic strokes and most of the standard guidelines recommend aspirin (class II evidence). RCPCH UK childhood stroke guidelines recommend 5mg/kg of aspirin up to a maximum of 300 mg within 24 hours of diagnosis of AIS in the absence of contraindications (e.g. parenchymal hemorrhage). After 14 days, the dose of aspirin is reduced to 1mg/kg to a max of 75mg.¹⁸ There is growing evidence for antiplatelet agent like clopidogrel in children and is claimed to be comparable to aspirin. It should be noted that aspirin has to be avoided during viral illness like influenza and varicella due to the risk of Reye syndrome. Vaccination for varicella and annual influenza vaccine should be encouraged.

b. Anticoagulant therapy: Heparin / Low molecular weight heparin (LMWH) is indicated in AIS in high risk group-arterial dissection, cardio-embolic stroke and hypercoagulable states. Often LMWH is initiated at the time of diagnosis of AIS and is given until the above 3 conditions are ruled out.^{17,18} The dose of low molecular weight heparin (Enoxaparin): 1 mg/kg/dose q12h (SC)

c. Recanalization therapy: Recanalization therapy is either by acute thrombolytic therapy or mechanical thrombectomy

d. Acute thrombolytic therapy: Current pediatric views on the use of acute thrombolytic therapy is controversial. An individually tailored approach should be considered (Box.7). Below are the recommendations based on two different recent pediatric reviews.

A latest pediatric review in 2019¹¹ states intravenous thrombolysis can be considered in children (1month to

Box.7 Evidence regarding thrombolytic therapy for childhood stroke

Class III Recommendation

Until there are additional published safety and efficacy data, tPA is not recommended for AIS outside of a clinical trial. Class III, Level of Evidence C

(Remember however there is **Class II Recommendation supporting and considering** thrombolytic therapy with tPA in selected children with venous stroke due to CVST. There is more supportive evidence for intravenous thrombolysis in venous ischemic stroke than arterial ischemic stroke in children)

18 years) who fulfill adult guidelines criteria, especially when one of these criteria is present; (i) occlusion of main arterial trunk, (ii) major thrombophilia, (iii) cardiac or artery-to artery embolism and (iv) basilar occlusion with clinical and imaging signs of severity.¹¹

RCPCH UK childhood stroke guidelines in 2017 mentions the off label use of tissue plasminogen activator (tPA).¹⁸ It could be considered in children presenting with AIS who are more than eight years of age and may be considered for children aged between two and eight years of age on a case-by-case basis when the following criteria have been met:

AIS has occurred as defined by

- (i) acute focal neurological deficit consistent with arterial ischemia AND
- (ii) Pediatric National Institute of Health Stroke Scale (PedNIHSS) more than or equal to 4 and less than or equal to 24 AND
- (iii) Treatment can be administered within 4.5 hours of known onset of symptoms AND
- (iv) Intracranial hemorrhage has been excluded (either a or b):
 - a) CT and CTA demonstrates normal brain parenchyma or minimal early ischemic change and CTA demonstrates partial or complete occlusion of the intracranial artery corresponding to clinical or radiological deficit OR
 - b) MRI and MRA showing evidence of acute ischemia on diffusion weighted imaging plus partial or complete occlusion of the intracranial artery corresponding to clinical or radiological deficit provided that there are no contraindications (DELPHI)¹⁸

II. Mechanical thrombectomy

Mechanical thrombectomy may be considered for acute ischemic stroke due to large vessel occlusion (ICA terminus, proximal middle cerebral artery/

M1 segment, basilar artery) in patients aged 1-18 years (Level C evidence, Class IIb recommendation).¹⁹

Although the role of recanalization therapy/ intravenous thrombolysis is established in adult stroke, its role is controversial in pediatric stroke.

Long term management

A. Neurorehabilitation and seizure control in case of epilepsy

Childhood stroke survivors need to have a structured neurorehabilitation program targeting the adverse physical, adaptive, cognitive, language, behavioral outcome and more than half of childhood stroke survivors have long term neurological impairment if left without neurorehabilitation. Residual motor impairment is common following ischemic stroke and measures to reduce spasticity of limbs like physiotherapy and giving anti spasticity drugs is extremely important. Epilepsy occurs in 30% of children following stroke and hence achieving seizure control is extremely crucial for better outcome

B. Secondary prevention

Stroke and TIA recurrence ranges from 7 to 35% in long term. Hence, secondary prevention of stroke is the most important aspect of long term management.

Antiplatelet therapy: Aspirin at a dose of 1 to 5 mg/kg/day is started in all causes of ischemic stroke except cardio embolic stroke, arterial dissection and hypercoagulable states and continued for a period of two years which is the time of highest risk for recurrent stroke. However, the optimal duration of treatment must be individualized. Remember antiplatelet therapy is routinely not needed in children with arterial ischemic stroke due to sickle cell disease for secondary prevention and management of stroke due to sickle cell disease is unique.

Anticoagulant therapy: Warfarin is the most effective means of prolonged anticoagulation in children and one of the options for secondary prevention (Class IIa, Level of Evidence C). However, it takes few days to have action.

Hence, low molecular weight heparin is initially given followed by switch over to oral warfarin. Target INR aimed is between 2.0 and 3.0 (The target INR is 2.5 to 3.5 in children with mechanical valves).^{17, 18} Warfarin is recommended for use in cardio-embolic stroke due to congenital or acquired heart disease, hypercoagulable states and arterial dissection.^{17, 18}

C) Specific treatment of underlying cause

- Regular periodic blood transfusions is given to maintain HbS below 30% in sickle cell disease. However due to long term adverse effects of periodic blood transfusions, HLA matched bone marrow transplantation from the siblings is the best option.
- Surgical repair of congenital heart disease
- Steroids and immunosuppressive therapy for primary CNS vasculitis
- EDAMS (Encephalo-duro-arterio-myo-synangiosis) or EDASS (Encephalo-duro-arteriosynangiosis) is the treatment done for Moyamoya disease.¹⁷
- Evidence regarding specific therapy in childhood stroke is listed in Box 8.

Venous ischemic stroke due to cerebral venous sinus thrombosis (CVST)

- Venous sinus thrombosis can affect deep venous sinuses or the superficial venous sinuses and the clinical presentation differs based on the system affected. The clinical manifestations are diverse and can be subtle and can often be missed. Increased

awareness regarding this condition is needed as they are often potentially treatable.

- Venous sinus thrombosis is often seen as a complication of common childhood illnesses like otitis media, head injury, meningitis. Other risk factors include dehydration, nephrotic syndrome, hyperhomocysteinemia, local or systemic infections, malignancies, recent intracranial surgery, drugs like L asparaginase induced prothrombotic states.
- Venous sinus thrombosis should be suspected in a child with altered sensorium, unexplained coma, stroke like episodes, new onset seizures, headache, vomiting, raised intracranial pressure, cranial nerve palsies
- MRI brain with MR venography confirms the diagnosis of venous sinus thrombosis. CT brain with contrast can also confirm the diagnosis and can be an option in places where MRI is not available. CT brain with contrast shows an empty delta sign in sagittal sinus thrombosis where as plain CT brain reveals a delta sign (dense triangle/cord sign).
- Mainstay of treatment is by administering low molecular weight heparin (LMWH) or unfractionated heparin (UFH) followed by switch over to oral warfarin to maintain long term anti coagulation with a target INR of 2 to 3. Anticoagulation with LMWH or UFH for at least 5 - 10 days, followed by warfarin or LMWH is suggested for a minimum of 3 months up to 6 months for CSVT in children if there is no significant hemorrhage. Radiological assessment for recanalization can be performed at 3 months. If recanalization is complete, anticoagulation therapy can be stopped.²⁰
- In case of CVST with significant hemorrhage, radiological monitoring of the thrombosis at 5 - 7 days is recommended; anticoagulation is suggested if thrombus extension is noted.²⁰
- Duration of anti -coagulation depends upon etiology and sometimes it may be required lifelong.
- Specific treatment for dehydration, nephrotic syndrome etc., has to be instituted. In case of hyperhomocysteinemia, administration of folic acid, pyridoxine and vitamin B12 is essential

Hemorrhagic stroke

- Approximately 50% of childhood strokes are hemorrhagic in origin in contrast to approximately 15% in adult strokes
- Hemorrhagic strokes are of two types:

Box.8 Evidence based specific therapy for pediatric stroke

Class I Recommendations

Individuals with Fabry disease should receive alpha galactosidase replacement therapy. (Class I, Level of Evidence B)

Class II Recommendations

1. Seek and treat iron deficiency because it may increase the risk of AIS in conjunction with other risk factors.
2. Measure the serum homocysteine level of children with CVST or AIS and institute measures to lower the homocysteine level when it is higher than normal. (Diet or supplementation of folate, vitamin B6, or vitamin B12.)

Intraparenchymal hemorrhage and subarachnoid hemorrhage

- The major cause for hemorrhagic stroke is vascular malformations which includes arterio venous (AV) malformations, aneurysms and cavernomas (hence look for any hemangiomas or vascular / neurocutaneous marker on general examination).
- Drug induced: phenyl propanolamine (nasal decongestant), cocaine and other illicit drugs.
- Hypertension could be a predisposing factor rarely but not prominent as in adults.

Risk factors¹⁷

- Intracranial vascular anomalies (48%): AVM, cavernous malformations, aneurysms
- Hematologic abnormalities (10%–30%)
- Thrombocytopenia, hemophilia, Von-Willebrand disease, coagulopathy secondary to hepatic dysfunction or vitamin K deficiency, iatrogenic due to heparin/warfarin therapy
- Brain tumors (9%)
- Idiopathic (19%)

Clinical presentation haemorrhagic stroke is shown in Table VII.

Table VII. Clinical presentation of haemorrhagic stroke

Intraparenchymal hemorrhage	Subarachnoid hemorrhage
Seizures, vomiting, rapidly developing progressive focal neurological deficit, altered sensorium (rapid drop in conscious state, from normal even to a comatose state), signs of raised intracranial pressure	<ul style="list-style-type: none"> • Sudden catastrophic event that may be preceded by sentinel headaches • Severe, first in a lifetime worst headache followed by sudden onset vomiting and altered sensorium

Diagnosis

- A strong index of suspicion is required to make the diagnosis of hemorrhagic stroke clinically. Spontaneous bleed in the absence of coagulopathy in the setting of AVM is challenging to diagnose at the time of first assessment.
- In an acute setting, CT brain is often the investigation done first and will detect the bleed in majority of children but the etiological yield is low. CT scan of brain shows hyper-density in the left intra-parenchymal region suggestive of hemorrhagic stroke in Fig.3.
- Although conventionally many think MRI brain detection rate to pick up bleed is poor compared to



Fig.3. CT scan of brain shows hyper-density in the left intra-parenchymal region suggestive of hemorrhagic stroke.

CT brain, the role of susceptibility weighted imaging (SWI) sequence of MRI brain has changed the dynamics and is a promising option.

- CT brain with CT angiography along with MRI brain including SWI sequencing is often the neuroimaging of choice in a child with suspected hemorrhagic stroke. Digital subtraction angiography (DSA) is done in advanced centers and its diagnostic yield is excellent. There is no clear cut consensus regarding the exact timing of these tests in any standard guidelines and decision is often clinical and based on feasibility.

Treatment

- Immediate stabilization and supportive care (as mentioned in arterial ischemic stroke)
- Administering vitamin K, fresh frozen plasma or recombinant clotting factor therapy depending on the scenario
- Neuro-radiological interventions/ Surgical repair of AV malformations and aneurysms.

Points to Remember

- *Consider stroke in any child presenting with acute onset hemiparesis or focal deficit, change in mental status, headache, seizure or speech disturbance.*

- ***MRI brain with MRA is the investigation of choice, but it is recommended at least that a CT brain is performed within one hour of arrival at hospital in every child. MR venography is done if cerebral venous sinus thrombosis is suspected.***
- ***Aspirin has to be started in all cases of arterial ischemic stroke as soon as possible in the absence of contraindications except arterial dissection, cardio-embolic stroke and hyper-coagulable states.***
- ***In CVST as well as in AIS caused by arterial dissection, cardio-embolic stroke and hyper-coagulable states, anticoagulation using LMWH (enoxaparin) / un-fractionated heparin or oral warfarin is used.***
- ***Role of thrombolysis in pediatric age group is controversial, however, there is growing evidence and looks promising.***

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