INTRODUCTION
Stroke in children is not a rare disease. It is much more common than what is expected. In one study, incidence of paediatric stroke was found to be 1.2-13/100,000 under 18 years of age.\(^1\) It is described as sixth leading cause of death in children in some of the studies.\(^2\) Stroke can occur at any age, even in the neonatal age. A large study done in five continents with a large cohort of cases, the median age of presentation of stroke in children was found to be 5.7 years.\(^3\)

However it is clearly evident that incidence of stroke has been doubled than previous over a period of decade. This may be because of increased survival of patients with stroke or increased recognition over a period of time with discovery of new techniques to diagnose.\(^4\) Gender variation for prevalence of stroke does occur in
children as it is more common in males as compared to females.\textsuperscript{5} This male predominance was recently studied in China and 70% of stroke was found to be present in males.\textsuperscript{6} But interestingly another study done in England, sex was not associated with increased risk of stroke but age and race are associated with increased incidence as it is more common in younger age and more in Asian and blacks than white.\textsuperscript{7}

**METHODS**

We searched stroke in PubMed and found 15315 articles, narrowed down to stroke in children (3814) and selected 45 articles for review. The time period chosen was from year 2000 to 2020. All the articles were read and relevant information was extracted from them to present in this review.

**CLINICAL PRESENTATION**

Clinical presentation of pediatric stroke is quite variable. Based on type of stroke and age of presentation, it ranges from focal deficit, fits to unconsciousness. Various studies have mentioned presentation of stroke. Focal neurological deficit in the form of hemiplegia is the most common presentation of pediatric stroke especially in arterial ischemic stroke which may be present up to 94% of cases.\textsuperscript{8}

Haemorrhagic strokes present more suddenly with headache in older children or with altered sensorium and vomiting in younger children. These features are not usually present in ischemic strokes.\textsuperscript{9} Presentation with seizures in paediatric stroke is not restricted to any specific type of strokes. They are usually present in both ischemic and haemorrhagic strokes and neither they are type specific nor age dependant. Seizures may occur up to 50% of cases.\textsuperscript{10}

Also stroke presentation not only depends upon type of stroke but also on a very important factor affecting or modifying the presentation is age. Different age groups have different presentation of strokes. The younger the patient is, the more nonspecific presentation may be. Younger patients usually present with irritability, lethargy, vomiting and fits. They may have bulging anterior fontanel showing signs of raised intracranial pressure.\textsuperscript{11}

While older children usually present with focal neurological deficit associated with altered conscious level, headache, vomiting and may be fits. They may have also complaints of visual loss, speech problems and walking difficulty.\textsuperscript{12}

**LOCALIZATION OF LESIONS**

The treating physicians and neurologists have always been interested to know the exact area of involvement in brain causing signs and symptoms. For the exact localization of lesions, one must be familiar with anatomical areas of brain, their physiological functions and moreover their blood supply. Depending upon area of involvement and their blood supply, level of lesions can be identified easily.

Focal neurological deficit is usually classified as:

1. Uncrossed hemiplegia
2. Crossed hemiplegia

This classification is based upon involvement of cranial nerve particularly of facial nerve. If focal neurological deficit and the cranial nerve are involved on the same side, then this is called uncrossed hemiplegia and it is said that the lesion would be present in supratentorial area above the brainstem. In this case affected area of brain anatomically would be opposite to the hemiplegia. While on the other hand, if hemiplegia is present in one side of body and cranial involved is present in opposite side of body, the lesion is described as crossed hemiplegia and lesion is present in infratentorial area at the level of brainstem. In this case lesion would be on the same side of brain which have cranial nerve palsy.\textsuperscript{13}

Apart from above mentioned, clinical sign and symptoms may reflect the particular anatomical area of brain involvement and can help to find artery involved as well. If there is involvement of left internal carotid artery (ICA), anterior cerebral artery (ACA), or middle cerebral artery (MCA) there would be right sided limb motor weakness, Aphasia, right limb weakness, right limb sensory loss, right visual field defect, reduced right conjugate gaze, difficulty reading, writing, and calculating. Similarly if there is involvement of right ICA, ACA, and MCA then there would be left limb weakness, sensory loss along with difficulty in drawing and copying. Speech will be spared if patient is right handed. In posterior cerebral artery (PCA) involvement, more of sensory symptoms are there like visual field defects, recognition of colours and objects. While in case of vertebrobasilar artery involvement, vertigo, diplopia, headache, crossed motor weakness, ataxia are usual clinical presentations. Involvement of internal capsule usual causes pure motor weakness and dense hemiplegia.\textsuperscript{8}

**RISK FACTORS AND CAUSES OF STROKE**

Although many risk factors and causes of stroke in children are attributed to many underline diseases like congenital heart disease, hematological disorders, CNS infections etc. but still certain percentage of patients...
with stroke are left with no underline diagnosis making it quite difficult for treating physicians to understand pathogenesis and etiology of pediatric strokes. In International Pediatric Stroke study (IPSS) which was done in five continents to include different races, regions and environmental factors and in many other stroke studies of children, many underline diseases have been recognized as a cause of stroke like sickle cell disease, cardiac disorders, major infections like meningitis, sepsis and encephalitis.14

There is an interesting fact that in IPSS, no identified risk factor was found in 9% of population. The risk factors identified in this study include arteriopathies (53%), cardiac disorders (31%), infection (24%), acute head and neck disorders (23%), acute systemic conditions (22%), chronic systemic conditions (19%), prothrombotic states (13%), chronic head and neck disorders (10%), atherosclerosis-related risk factors (2%), and other (22%). Many patients had more than one risk factor as Fifty-two percent had multiples risk factors as well.15 In another study 25% of children had multiple risk factors which shows the need of more aggressive and prompt investigation to identify these risk factors.15

**Cardiac**
Cardiac diseases both cyanotic and acyanotic can lead to stroke in children and it is the most common cause of stroke in children. About one third of all arterial ischemic strokes are due to cardiac lesions. Stroke related to congenital heart disease are usually because of embolic phenomenon which results either from dysfunctioning of ventricles, clot, vegetation or damaged valves because of rheumatic heart disease. In case of long standing cyanotic heart diseases, there is anaemia and polycythaemia which leads to increased risk of thromboembolic phenomenon. Moreover, in perioperative conditions there is high risk of ischemic stroke upto 50% in children.16

**Hematological disorders**
There are many hematological disorders in children which can cause both arterial ischemic strokes as well as hemorrhagic strokes. Among them, sickle cell disease is a very important risk factor for strokes. In one study it was found that 285 cases per 100,000 of stroke occurring in affected children because of sickle cell disease. It can occur as early as 18 month of age but usually occur after five year of age. Ischemic stroke are more common in sickle cell disease as compared to hemorrhagic stroke. Exact pathogenesis is unclear but microcytic anaemia, sticky RBC’s and stasis may be involved in stroke.17

Other disorders like prothrombotic condition can also cause stroke but usually these disorders lead to venous thrombosis and subsequently venous infarction like protein C, S and Antithrombin iii deficiency. On the other hand bleeding disorders like factor viii, factor vii, factor ix deficiency cause hemorrhagic strokes in children.18 Vascular malformations may cause stroke (especially hemorrhagic stroke). Sturge-Weber syndrome, Neurofibromatosis and von Hippel Landua disease have strong association with malformations.19

**Infections**
Stroke may be a frequent complication among central nervous system infections (bacterial, viral, tuberculous or fungal). These are usually ischemic strokes secondary to local vasculitis being caused by infection. Tuberculous meningitis is associated with many neurological complications such as hydrocephalus, cranial nerve palsies, mental retardation and stroke etc. In a study done in adults stroke was found to be present in 25% of cases.19

In another study done for community acquired bacterial meningitis in adults to see frequency of stroke, about 14% of cases were having stroke, majority with ischemic strokes. Viral encephalitis particularly varicella zoster can cause many complication including ischemic strokes. In varicella zoster infection, even months later, AIS can occur secondary to vasculopathy caused by this virus.20

**Trauma**
Accidental trauma or trauma secondary to some surgery can lead to stroke both ischemic as well as haemorrhagic. Head and neck trauma in children particularly can result in stroke. This causes vascular injury within walls of vessels and then result in thromboembolic phenomenon and stroke. Otherwise stroke in trauma is usually haemorrhagic in nature.21

**Arteriopathies**
Arteriopathies have been described as focal or segmental narrowing or occlusion of arterial blood vessels with irregularities in vessel walls. Arteriopathies is now being considered as the most common cause of arterial ischemic stroke in children. The frequency of cerebral arteriopathy in published reports varies from 53–86%.22

In an International Pediatric Stroke Study including 667 children done over five continents, arteriopathies was considered the most common risk factor for AIS. In this study 53% of cases undergoing neuroimaging was found to have arteriopathy. Some arteriopathies have
well recognized predisposing factor such as moyamoya, sickle cell disease, arterial dissection etc. But in this study, about 30% of cases presenting as a first case of AIS and angiography shows a focal stenosis of occlusion of blood vessel without underlying risk factor for stenosis. Such patients should undergo extensive work up and must be followed for next 6-12 months of period to see the clinical course on repeat angiography either magnetic or computed angiography (MRA or CTA).²³

There are different types of arteriopathies and diagnostic criteria has been made which was first laid down by Se´bire G and his colleagues in 2004 for moyamoya, vasculitis, dissection, transient cerebral arteriopathy (TCA) and post varicella arteriopathy (PVA).²⁴

TCA was first described in 1998 as a unilateral narrowing of stenosis of intra cranial part of Internal carotid artery (ICA) or of middle cerebral artery (MCA). TCA in times may become stabilized or improved. When TCA is preceded by varicella infection 12 months or more prior to stroke, then it is labelled as post varicella arteriopathy (PVA).²⁵

In IPSS and in other studies, TCA is strictly implied to monophasic course of illness with unilateral involvement. It has also been emphasized that sile at time of presentation focal narrowing identified by angiography cannot be taken as a manifestation of arteriopathy, repeated or follow up scans and angiography are mandatory to confirm TCA or progressive arteriopathy with bilateral involvement. If 6 month later angiography shows unilateral involvement with either stabilized lesion or improved than previous with focal or segmental narrowing of the same side, then it is labelled as focal/ transient arteriopathy (TCA). On the other hand, if repeated scan shows worsening of lesion in the form of progressive narrowing/ occlusion compared with the previous one or bilateral involvement with multiple vessels then it is called progressive arteriopathy.²⁶

Focal cerebral arteriopathy
Focal cerebral arteriopathy (FCA) is considered to be most common arteriopathy among all. In the recent study done as IPSS in 2009, FCA was found to be present in 25% of cases out of 525 investigated cases for pediatric stroke. In this study, recent upper respiratory tract infection was the major predictor of FCA.²⁷

While in another study done again in 2009 including 79 children with idiopathic stroke and went under extensive investigation and long term follow, FCA was present in 94% of cases while only 6% had progressive arteriopathy. In this study, arteriopathy having previous history of varicella infection 12 months or more has been described as post varicella arteriopathy (PVA) which was present in 23% of all FCA. However the term FCA/TCA are just descriptive having same meaning with unilateral involvement strictly and on follow either having stabilized or improved lesion although transient worsening of lesion may occur initially during six month follow up.²⁸

Initially varicella infection was found to be linked with focal cerebral arteriopathy as shown in study done by k. Braun et al and described it as post varicella arteriopathy PVA instead of FCA.²³

Moreover to look for any risk factor including infections for FCA, IPSS studied over a very large cohort of patients in five continents and found an association between minor prior infection and FCA. Other predictors for overall arteriopathies were recent upper respiratory tract infection, early school age and sickle cell disease.²⁹

DIFFERENTIAL DIAGNOSIS
Stroke is a focal neurological deficit that persists more than 24 hours and many disorders or conditions can be confused with stroke. The important differential is post seizure focal deficit usually called Todd’s paralysis mainly after focal seizure. However infectious causes and any brain tumour for focal seizures with prolonged neurological deficit should be considered. Another important condition is migraine which can cause even alternating hemiplegia and must be considered in the differential diagnosis.³⁰

EVALUATION OF STROKE IN CHILDREN
Diagnosing paediatric stroke has always been remained difficult for treating physician especially in case of children because of nonspecific sign and symptoms. Diagnosis of AIS is based upon both clinical suspicion and a broad differential diagnosis which mimic with stroke. Therefore one should have very high index of suspicion keeping in mind the variable presentation of stroke in children. Delay in diagnosis has been there in adults and many contributing factors are associated. But in children delay is even more which not only miss the diagnosis but also result in failure of timely management.

Since more than one risk factor may be associated for stroke, evaluation of patients with stroke needs
detailed history and thorough examination to look for any risk factor leading to focal neurological deficit.

Every child with stroke should have base line investigation with complete blood count, coagulation profiles, cardiac evaluation especially if already having structural heart disease, tests for thrombophilia, and for autoimmune diseases. Angiography should be performed as per protocol and its importance is being recognized day by day. Some centres have made their protocols for vascular imaging of head and neck, echocardiography and thrombophilia tests regardless of prior known risk factors. Basic tests needed for a stroke patient are highlighted in Table 1.31

### TABLE 1: Investigation to be Considered for Acute Pediatric Stroke

<table>
<thead>
<tr>
<th>Complete blood count with peripheral smear</th>
<th>Special test when indicated</th>
<th>Brain neuroimaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulocyte count</td>
<td>Lupus anticoagulant</td>
<td>CT brain non contrast and with contrast as per condition</td>
</tr>
<tr>
<td>ESR, CRP, ANA</td>
<td>Anticardiolipn antibody</td>
<td>MRI</td>
</tr>
<tr>
<td>Coagulation profile</td>
<td>Protein C,S &amp; antithrombin III level</td>
<td>MRA</td>
</tr>
<tr>
<td>ECG, CXR &amp; cardiac evaluation</td>
<td>Factors level for bleeding disorder</td>
<td>MRV</td>
</tr>
<tr>
<td>S/cholesterol, triglyceride</td>
<td>Echocardiography</td>
<td>CT angiogram</td>
</tr>
</tbody>
</table>

### ROLE OF NEUROIMAGING

Neuroimaging used for stroke can be CT brain both contrast and non-contrast, vascular imaging is the basic investigation to look for any etiological factor related to cerebral blood vessels. In IPSS, 53% of all cases were found to have arteriopathies based upon vascular imaging by magnetic resonance angiography.32

Non contrast CT is usually the first modality to use for acute stroke as it has high sensitivity for haemorrhagic stroke upto 93% especially for subarachnoid hemorrhage. Urgent CT is also required to differentiate between ischemic stroke and haemorrhagic stroke.33 In case of AIS, initial CT may be normal if performed within 12 hours of onset of sign and symptoms and in that case MRI is more sensitive to pick ischemic damage than CT.

Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) should be performed to identify exactly the arteries and vessels in details for vascular pathology, CTA can also be a good modality for evaluation of blood vessels especially any dissection of arteries. However contrast to be used and high exposure of radiations can be the limitations of this diagnostic test and moreover availability may not be present at every centre.34

### MANAGEMENT

The management of acute stroke in children include initial supportive treatment in emergency and then specific therapy for stroke depending upon type of stroke and its etiology cause followed by long term management such as preventive measures, physiotherapy and rehabilitation.

**Acute management**

High index of suspicion and then prompt action to manage the condition is required as any delay in diagnosis can lead to high rate of mortality and morbidity. Studies in adults have shown good outcome when interventions in the form of thrombolytic agents have improved the outcome but such interventions have very narrow window period to intervene (usually within 6 hours of onset of symptoms).35
Management of patients can be done in following three steps
1. Supportive care
2. Diagnostic modalities in emergency
3. Specific therapy

General measures include control of fever, control of seizures, normalization of serum glucose level, maintenance of normal oxygenation, control of systemic hypertension, care of bowel and bladder and control of raised intracranial pressure which at times can be very lethal if left untreated. Control of raised intracranial pressure (ICP) needs correction of hydration, restriction of fluids, raise head end to 30 degree, osmotic diuretics, hypothermia and any surgical intervention if required. There is no evidence for use of anticonvulsant prophylactically in absence of clinical or electrophysiological evidence of seizure.36

Type specific management of stroke

Further management of children depends upon the type and aetiology of stroke. Usually the management of stroke in children is guided on the basis of ischemic stroke or haemorrhagic stroke.

Management of arterial ischemic stroke

Just to highlight the importance of early diagnosis and prompt action to take, stroke is being labelled as BRAIN ATTACK just like the heart attack. This is because of narrow window period during which if intervention are carried out, outcomes improves remarkably.

After the confirmation of ischemic stroke and supportive treatment, the most important next step is initiation of anticoagulation therapy to prevent further ongoing damage and to reduce the risk of recurrence. The choice of anticoagulation in children is centre specific and it may be either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) in continuous infusion. Either of these two can be used and studies have shown no difference in outcome.

Anticoagulation can also be given in pending stroke and outcome has been found better than those without anticoagulation.37

Anticoagulation in children are used for stroke caused by arterial dissection, vasulopathies, cyanotic heart diseases, thrombophilia, cerebral venous sinus thrombosis, and progressive deterioration of clinical condition in newly diagnosed cerebral infarction. The protocol and dosage of anticoagulant in children is given in table 2 and 3.

Anticoagulation therapy is usually continued for 7-10 days. Before the stoppage of parenteral anticoagulation, long term therapy can also be started either in the form of antiplatelets agents i.e asprin or clopidgrol or oral anticoagulant like warfarin. For coagulation disorders or venus sunus thrombosis, oral anticoagulants like warfarin can also be started. The monitoring of patients taking warfarin should be monitored with INR and dose has to adjusted according to the desired INR level. The protocol about use of anticoagulants in emergency is being mentioned in Table 2 and 3.38

### TABLE 2: Protocol for Using LMWH in Children

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Initial treatment dose</th>
<th>Initial prophylactic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>body weight-dependent dose, units/kg per 12 h</td>
<td></td>
</tr>
<tr>
<td>&lt;5 kg</td>
<td>150</td>
<td>50</td>
</tr>
<tr>
<td>&gt;5 kg</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin, age-dependent dose, mg/kg per 12 h</td>
<td></td>
</tr>
<tr>
<td>&lt;2 month</td>
<td>1.5</td>
<td>0.75</td>
</tr>
<tr>
<td>&gt;2 month</td>
<td>1.0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

LMWH: Low-molecular-weight heparin
TREATMENT PROTOCOL FOR CHILDHOOD ARTERIAL ISCHAEMIC STROKES (AIS) WITH PROVEN ARTERIOPATHIES

As arteriopathies are emerging as a common cause of arterial ischemic stroke and studies have shown some immune mediated pathogenesis, therefore certain centres have made protocols to treat proven arteriopathies aggressively. This protocol is described as below.

Induction therapy: 5-10 days
• Methyl prednisone 25 mg/kg intravenous over 4 hours daily for 3 days and/or intravenous immunoglobulin 400 mg/kg/day over 6 hours for 5 days.
• Oral prednisone 2 mg/kg daily (maximum 60 mg daily) for 30 days, weaning over 30 days.
• Supplementary calcium and vitamin D also given during prednisone treatment.
• Heparin (for ischaemic strokes, infarction size 50% of cerebral hemisphere size); loading dose 75 units/kg intravenously followed by 20 units/kg/hour for children over one year of age (or 28 units/kg/hour below one year of age) for 3-5 days, followed by oral anticoagulants for 30 days.
• Low molecular weight (LMWH)
• Anticonvulsants and antipsychotics as needed.
• Antibiotics and antiviral and antacids along with other supportive cares as needed.

Maintenance therapy: 24 months
• Aspirin 3 mg/kg daily for all ischaemic strokes.
• Aspirin 3 mg/kg and azathioprine 1 mg/kg daily for progressive arteriopathies.
• Anticonvulsants, antipsychotics, nutrients and other supportive cares as needed.

ROLE OF THROMBOLYTIC THERAPY IN CHILDREN FOR AIS

Although thrombolytic therapy has been commonly used in adults with ischemic stroke, its role in children is still under clinical trials. Different centres have tried the use of thrombolytic agents in selected patients but their safety in children requires large multicentre trials for clear guidelines. Although there are certain case reports and case series published regarding the use and safety of thrombolytic agents like IV tPA for AIS in children but guidelines with consensus are still be awaiting.

The use of tPA in children has to be very careful and it is not without some serious complications. Many studies have shown major complication including cerebral hemorrhage after the use of tPA for ischemic stroke.

MANAGEMENT OF HEMORRHAGIC STROKE

General supportive treatment is same for both ischemic and haemorrhagic stroke. Apart from surgical intervention for certain types of haemorrhagic strokes, nothing much can be done. Medical management which can be offered includes transfusion of clotting factors if they are deficient. Implementation of clotting
factors not only stop the rebleeding but also helps to stop fresh bleed through maintaining haemostasis and reducing hemorrhage volume. Surgical intervention which can be done for haemorrhagic stroke is the evacuation of haematoma. There are variable results of outcome after surgical evacuation. A meta-analysis study done showed however clear evidence of benefit of surgical evacuation in terms of being dead or dependent. Other surgical options include stereotactic radiosurgery, microsurgical or endovascular techniques, and endoscopic surgical evacuation of the intracerebral hematoma or obliteration of aneurysms and AVMs. Another surgical consideration is emergent splenectomy for intraparenchymal bleeding associated with idiopathic thrombocytopenic purpura.41

OUTCOME OF PAEDIATRIC STROKE
Population based and hospital based studies have been done to estimate the mortality and morbidity associated with arterial ischemic in children. The mortality because of AIS in children was found to be 16-20%.42

With the advancements in technology and new treatment modalities, the mortality with AIS has decreased over past years. However the sequel developed after ischemic insult to brain is now being observed to be increasing because of increased survival rate. Cognitive dysfunction, poor quality of life and motor deficit are present in more than 50% of cases. There are many factors affecting the outcome after ischemic stroke. Young age, male gender and bihemispheric infarction are associated with poor outcome.43

HEMORRHAGIC STROKE OUTCOME
The death related to haemorrhagic stroke (HS) is found to be higher as compared with AIS in some studies although little data available for children in this regard. Non- population based studies are there to estimate the mortality and found to be 25% in HS.44 While individual studies show mortality ranging from 7 to 54%.And only one study which is population based has given mortality of HS as 5.2%.44

RECURRENCE OF PAEDIATRIC STROKE
Recurrence can be there in both AIS as well as HS. There are certain factors associated with recurrence and have been studied so that any preventive strategy can be adopted to prevent such recurrence. In California, study done showed 5 year cumulative recurrence rates of 1.2% after perinatal stroke and 19% after later childhood stroke. In this study, importance of neuroimaging has been highlighted to predict the recurrence. In this study it was found that although there were no recurrences among children with normal vascular imaging, children with a vascular abnormality had a 5-year cumulative recurrence rate of 66%. And this vascular abnormality was found to be a vasculopathy unilateral, bilateral or progressive. And in another study done to look for long term outcome of unilateral arteriopathies in AIS, it was found that 6% had progressive arteriopathy with either worsening of already existed focal deficit or appearance of new focal deficit indicating the importance of repeat neuroimaging.45

CONCLUSION
Stroke in children has major morbidity and mortality associated and is now being recognized more and more with the advent of new diagnostic modalities and treatment regimens. But still a lot of work has to be done especially for paediatric strokes to make a consensus guidelines for the diagnosis and management of paediatric strokes.

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**Tipu Sultan**: concept, data collection, data analysis, manuscript writing, manuscript review

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