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CONTENTS

TOPIC OF INTEREST - "NEUROLOGY "

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NEUROLOGY

FEBRILE FITS

***Kumaresan G**

Abstract: *Febrile fits is a common condition seen in day to day practice. The diagnosis is mainly clinical and there is limited indications for investigations. EEG often adds to confusion and is best avoided. The role of genetics is being recognised. Intracranial infections, febrile myoclonus, epileptic syndromes presenting initially as febrile seizures are to be considered in the differential diagnosis. Long term anti-convulsants should be avoided except in rare situations. Intermittent prophylaxis with clobazam is useful in reducing recurrences and parental anxiety.*

Keywords: *Febrile fits, Prognosis, Genetics, Differential diagnosis, Intermittent clobazam.*

Febrile fits is known from the days of Hippocrates. Convulsions occur in children with acute fever and most readily in those who are very young up to their seventh year. Despite the recent advances in genetics and neuroimaging, many questions remain unanswered. The prevalence is reported to be around 3-4% with a higher prevalence in some countries like Japan (7%) and Guam (14%).[1]

There have been differences between pediatricians and neurologists regarding long term prognosis. This is because of varied results based on epidemiological studies and retrospective studies. The most quoted epidemiological study is by Nelson and Ellenberg who followed up 1706 children with febrile fits up to 7 years of age and noted it to be a benign condition.[2] Similar results were noted by many others like Verity (1985) Vandenberg (1969).[3,4] The estimated risk of subsequent epilepsy as per these studies was around 1 in 75,000 children. However, the retrospective studies from neurosurgical centres have the power to detect rare events but not their frequency. It was noted that more than one third cases of intractable temporal lobe seizures undergoing surgery had history of febrile fits in childhood and is termed 'Meyer' hypothesis. This hypothesis suggests that prolonged febrile seizures leads to ischemia which in turn leads on to hippocampal sclerosis many years later.[5]

The advent of MRI has added more information. Fernandez followed up 23 members with family history of febrile fits with MRI. The interesting observation was hippocampal abnormalities were seen in 6 out of 10 children who never experienced febrile fits as compared to 6 out of 13 children with history of febrile fits.[6] Van Landingham study showed 2 out of 6 positive cases in children with complex febrile seizures had pre-existing abnormalities in hippocampus. Four children with prolonged seizures showed acute edema in hippocampus.[7] These studies established two points (i) pre-existing lesions in hippocampus may contribute both to febrile fits and subsequent development of epilepsy and (ii) prolonged seizures (of any etiology) can cause changes in hippocampus leading to epileptogenic focus years later. This was also observed in Febstat study which showed both acute injury and presence of pre-existing abnormalities twice more than in controls.[8]

Hippocampal sclerosis is seen in an epileptic syndrome called 'familial mesial temporal lobe epilepsy'. But this is also seen in their asymptomatic first degree relatives suggesting that hippocampal sclerosis is not related to seizure severity and may occur in individuals who never had seizures, indicating a genetic predisposition and the seizure severity being dependent on interaction of both genetic and environmental factors. So, the question which still needs to be answered is that if the pre-existing hippocampal sclerosis predisposes to both temporal lobe epilepsy and inconsequential febrile fits or childhood febrile status caused the initial damage leading to hippocampal injury. Thus hippocampal injury can be both the cause or effect of prolonged seizures–febrile status being one of the causes. The pre-existing lesions may act in three different ways - (i) hippocampal malformations may themselves cause both febrile fits and temporal lobe epilepsy, (ii) may increase the vulnerability to damage caused by febrile fits and (iii) may increase the vulnerability to damage by fever. There is no mention of febrile fits in 1969 classification in the International classification of

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Epilepsy. In 1981 classification, it is classified under special syndromes-situation related. In 2001 classification, it was 'seizures not necessarily requiring a diagnosis of epilepsy' while in 2014 the word "seizure" is replaced by 'epileptic event'.

Definition

National Institutes of Health (NIH) definition of febrile fits – 'an event in infancy or childhood usually occurring between 3 months and 5 years of age associated with fever but without evidence of intracranial infection or defined cause'.[9]

Types of febrile fits

1. **Simple febrile fits:** Brief single generalised seizures.

2. **Complex febrile fits**: Focal, prolonged (>15 minutes) and multiple seizure in a single febrile episode.

This differentiation is important in determining the recurrence rate and future epilepsy.

Status epilepticus and febrile fits

Twenty-five percent of status epilepticus in ER is due to febrile status. Five percent of febrile fits may present as status and may be the initial presentation. FEBSTAT study is an important study involving 299 children presenting with febrile status epilepticus. One-third of children with febrile status showed positive PCR or antibody titres for Human Herpes virus (HHV) 6B or 7.[8]

Genetics and febrile fits[10]

Febrile fits was initially considered to be inherited by dominant mode of inheritance with incomplete penetrance. Advances in genetics has led to recognition of many genes like FEB-1(on8q 13-21), FEB-2(19p13.3), FEB-3 (2q23-24), FEB-4(5q14-15) and R43q mutation (CARBG-2) to name a few, leading to recognition of larger role of genetic susceptibility.

There are a few epileptic syndromes associated with initial presentation as febrile fits.

(i) Generalised epilepsy with febrile seizures (GEFS+): This syndrome may continue beyond 6 years of age as multiple febrile fits and by several subsequent types of afebrile generalised seizures – generalised tonic clonic, absence, myoclonic, atonic or myoclonic astatic seizures with variable degrees of severity.

(ii) Dravet syndrome: This may present as early onset febrile fits before six months of age, prolonged febrile seizures and family history of multiple types of seizures. Development of focal or myoclonic seizures and developmental slowing, stagnation or regression in the second year of life suggests Dravet syndrome. Gene defect has been localised to SCN1A, SCN1B and GARBG-2.

(iii) Familial temporal lobe epilepsy: This may be associated with predisposition to febrile fits and other types of seizure.

Febrile seizures are believed to be caused by vagal mediated cerebral ischemic anoxia. This suggests that febrile fits resemble cerebral anoxic seizures and may occur without obvious epileptic mechanism.

Differential diagnosis

1. Benign febrile myoclonus: Myoclonic jerks with fever. This condition may be dramatic enough to be mistaken for other types of seizures including febrile fits and can lead to unnecessary investigations.[11]

2. Afebrile febrile seizures is a newly described entity. It is a distinct entity not related to febrile seizures. It is a provoked seizure lacking objective evidence of fever at the onset of seizures but have definite symptoms and signs of minor infection.[12]

Investigations

Observation of the child over next few hours is more important than rushing into admission to ICU, CT scan or CSF analysis. The combination of fever and seizures may be due to febrile seizures, intracranial infection, metabolic disturbances or initial presentation of an epileptic syndrome like Dravet syndrome or GEFS+ syndrome.

CSF analysis

American Academy of Pediatrics (AAP) has laid down criteria for CSF analysis in febrile fits. In children below 12-18 months of age, it is strongly recommended. However, this is not uniformly agreed. Pediatrician with experience can avoid CSF analysis without missing intracranial infection. Kimia reported no case of meningitis in 271 children of 6-18 months of age presenting with febrile fits.[13] However, one has to remember that the chances of intracranial infection may be as high as 15-18% in febrile fits presenting as status. Other indications for CSF analysis include prior antibiotic therapy and presence of sepsis elsewhere like skin or ear. Though 5% of children with intracranial infection may present with fever and seizures, prolonged duration of seizures, focal neurological deficit and prolonged duration of unconsciousness will be the red flags.

EEG

Though different patterns are described in the EEG of children presenting with febrile fits, none of these are specific for febrile fits, nor are they useful for prognosis. Often many non-specific changes or normal variants are reported as epileptic activity by the less experienced and may confuse the pediatrician.

Neuro-imaging

This is indicated in status epilepticus, focal seizures and presence of prior neurological abnormality but in many series it has been normal. EEG and neuro-imaging done unnecessarily can add to the cost of treating a child with febrile fits.

Prognosis

The recurrence of febrile fits is roughly one in three children. Two aspects are risk of recurrence and risk for subsequent epilepsy. Risk factors for recurrence of febrile fits are young age of onset, prior neurological abnormality, family h/o febrile fits, family h/o epilepsy, occurrence with low grade fever, short interval between onset of fever and seizure and complex febrile fits. The risk for epilepsy varies between 2-7% depending on the number of features of complex febrile seizures.

Treatment

The risk of side effects of long term anti-convulsants outweighs the benefits of treating a benign self limiting condition. Parents have to be counselled about the benign nature of febrile fits. Each episode may appear to them as life threatening event. They should be taught about first aid measures in handling a convulsing child at home and prehospital management of seizures persisting beyond 5 minutes with rectal diazepam (0.3-0.5 mg/kg to a maximum of 5 mg), intranasal midazolam 0.5 mg nasal spray (0.2-0.3 mg per dose divided into half on each nostril) or sublingual (oral soluble) lorazepam though not commonly used. Prompt reduction of fever will add to the physical comfort though its role in prevention of seizures is questioned.

The next most important point to remember is prolonged seizures of any cause which can lead to brain injury and enhance the subsequent risk of epilepsy. The present practical definition of status epilepticus is any child coming to ER convulsing or seizures lasting more than 10 minutes as against the old definition of status as seizures lasting for more than 30 minutes. Hence the best approach is to established an effective emergency management protocol for every convulsing child.[14] Parents and paramedical should be taught about pre hospital therapy with a benzodiazepine. Unfortunately this facility may not be available always. Routine long term maintenance therapy should be discouraged but may be needed in special circumstances like presentation as status every time, lack of accessibility to emergency medical care or frequent recurrences despite intermittent prophylaxis. The use of routine therapy must be discouraged. Phenobarbitone and sodium valproate have been used for continuous therapy. Phenytoin or carbamazepine are ineffective.

Intermittent therapy

During febrile illness initial intermittent therapy with oral diazepam has been used. Clobazam has less sedative effect. Intermittent use of clobazam (0.7mg/kg/day in three divided doses for 3-4 days) has been found to reduce the frequency of recurrences in many studies.[15] This may not be effective if the interval between onset of seizures and recognition of fever is very short or if seizures occur with low grade fever. Sedation and hyperkinesis may be undesirable effect. However, this mode of therapy is not mentioned in many text books. There is a recent article suggesting the use of intermittent melatonin in febrile seizures.[16]

In my practice, I counsel the parents the first aid and use of intra nasal Midazolam if seizures persist for more than five minutes. For prevention intermittent clobazam is useful. Continous anti convulsants is used only for prolonged febrile fits and repeated reccurences occur despite intermittent prophylaxis.

Points to Remember

- ***Febrile fits is a benign age related, self limiting condition.***
- ***Clinical observation to exclude other conditions is most important than investigations.***
- ***Early therapy to stop on-going seizure is important.***
- ***Hippocampal abnormalities can be both cause and effect of febrile fits in different situations.***
- ***Intermittent therapy is useful to minimise recurrences and parental anxiety.***
- ***Restrict use of continuous anti-epileptic drugs.***

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CLIPPINGS

The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health-The latest 2019 novel coronavirus outbreak in Wuhan, China.

Corona viruses (CoVs) are a group of RNA viruses which have posed a global threat to public health. They have an extensive range of natural host. A new corona virus, 2019-nCoV was identified in Wuhan, China after a cluster of cases with symptoms of "pneumonia of unknown cause" were reported. The virus has shown evidence of human-to- human transmission with escalating transmission rate. Now many cases are being reported worldwide. The incubation period of the virus is between 2 to 14 days which is a contagious period. The symptoms include fever, coughing and breathing difficulties; cases of severe infection can result in renal failure and death. Transmission of the virus occurs among close contacts via respiratory droplets.

The virus (2019 n-CoV) was first isolated from a patient in china on 7 Jan 2020 and genome sequencing of the virus was done and it became available to WHO on 12 Jan 2020, now worldwide specific diagnostic PCR tests for detecting the novel infection is available. Like SARS-CoV and MERS-CoV zoonotic infections, 2019 n-CoV was also related to zoonotic spread which was believed to be related to wild animals at the seafood market in Wuhan.

However there is very limited clinical information about the virus, pathogenesis, age range for infections, any treatment response to the virus and any available vaccines. The rapid identification and containment of the infection is reassuring and is a commendable achievement in the capacity to detect, identify and contain the new outbreak globally.

Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health-The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020; 91:264-266.

NEUROLOGY

STROKE IN CHILDREN

***Vykuntaraju K Gowda**
****Balamurugan Nagarajan**

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 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]

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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
- Sickle 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 mineralistation of lenticulostriate vessels.[16]

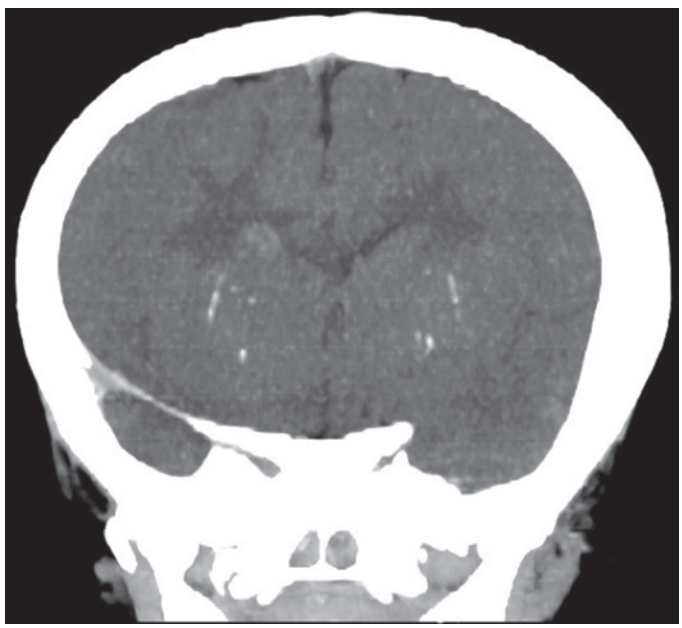

Fig.1. Coronal CT scan - Punctate micro calcifications in bilateral basal ganglia, in MALS.

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 resolved[11]

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 stroke[18]. 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 12th 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.

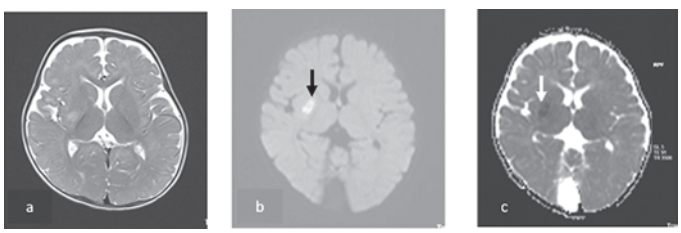

Fig. 2. Axial T2WI (a) Hyperintensity in right posterior putamen. DWI MR (b) and corresponding ADC mapping (c) Diffusion restriction in right posterior putamen in a child with mineralizing angiopathy of lenticulostriate arteries.

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 • 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 2019[11] 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 arterycorresponding 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. Neurorehablitation 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 1to5mg/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

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.)

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:

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 factors[17]

- 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.

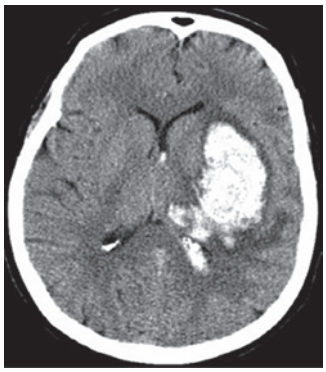

Fig.3. CT scan of brain shows hyper-density in the left intra-parenchymal region suggestive of hemorrhagic stroke.

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.

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	• 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

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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NEUROLOGY

ACUTE DISSEMINATED ENCEPHALOMYELITIS IN CHILDREN

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Abstract: *Acute disseminated encephalomyelitis is a demyelinating inflammatory disorder characterized clinically by acute-onset polyfocal neurologic deficits and encephalopathy and fluffy white matter lesions radiologically. Antecedent factors include infections, vaccinations and others. Usually, a monophasic illness, recurrences should raise a suspicion of a relapsing disorder such as myelin oligodendrocyte glycoprotein associated demyelination or multiple sclerosis. Investigations are warranted to rule out other causes of encephalopathy. Management includes immunomodulation with high dose pulse methylprednisolone, intravenous immunoglobulin and / or plasmapheresis. Prognosis depends on the recovery after the acute stage and the risk of recurrent demyelination.*

Keywords: *Demyelination, Acute disseminated encephalomyelitis, Myelin oligodendrocyte glycoprotein associated demyelination, Neuroinflammation.*

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder of the central nervous system (CNS). It is common in children and is usually regarded as a monophasic illness often heralded by infection. It is characterized by acute onset polyfocal neurologic deficits and encephalopathy clinically. Radiologically, fluffy demyelinating lesions in the white-matter of the brain and or spinal cord with or without involvement of deep gray matter are seen. The widely followed diagnostic criteria for ADEM were initially delineated by the International Pediatric Multiple Sclerosis Society Group in 2007 and revised in 2013 (Box 1).[1,2]

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Box 1. Diagnostic criteria for ADEM

- A first polyfocal clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy (unexplained by fever, systemic illness or post ictal symptoms)
- Brain MRI consistent with demyelination during the acute (less than 3 months) phase
- No new clinical or MRI findings 3 months or more after the clinical onset

ADEM is one of the childhood acquired demyelinating syndromes (ADS) which comprise a group of immune-mediated disorders of CNS. These include characteristic clinico-radiologic-pathological syndromes with neurological deficit and encephalopathy, features of CNS demyelination on neuroimaging and pathology.[1] ADS may be monophasic or recurrent. Monophasic ADS include ADEM (may be recurrent), optic neuritis (ON), transverse myelitis (TM) and clinically isolated syndromes (CIS). The recurrent ADS classically include myelin-oligodendrocyte-glycoprotein (MOG) associated demyelination, neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS).

Epidemiology

The incidence of ADEM varies from 0.3 to 0.6 per 100,000 children per year with a seasonal predilection for winter and spring.[3,4] The mean age at presentation is 3.6 - 7 years, with slight male predominance.[3-5] A viral infection usually precedes ADEM by two days to four weeks.[3,6] Other antecedent factors include vaccination such as influenza, polio, hepatitis B, rabies, measles, mumps, rubella, diphtheria, tetanus, pertussis, etc. It is important to note that besides ADEM, vaccination has also been associated with other demyelination syndromes such as Gullain Barre syndrome, optic neuritis and myelitis.[7] However, the causality of these associations is debatable and the association of an antecedent infection is much more common than a preceding vaccination.[3]

Pathophysiology

The exact etiopathogenesis of ADEM is unclear. The proposed hypothesis includes specific antibodies elicited after molecular mimicry such as anti-MOG antibody stimulating inflammatory cascade leading to demyelination. Additionally, B cell pathways, regulatory T cells and helper T cells have also been implicated.[3,8]

Clinical presentation, course and classification

ADEM has varied clinical presentations. The clinical course consists of a non-specific prodrome (fever, headache, etc., lasting for 3-4 days) followed by neurological symptoms.[3] The site of lesions determines the clinical features. Encephalopathy remains mandatory for the diagnosis of ADEM (Box 1). Other features may include fever, cranial nerve palsies, diminution of vision, seizures, paresis, pyramidal signs, cerebellar signs, etc. Although the maximum deficits are usually seen within 2-5 days, the clinico-radiological findings may evolve over the initial three months. The appearance of any new findings beyond three months is considered a second event. ADEM, though classically considered as a monophasic illness, maybe consequently diagnosed as an initial presentation of recurrent ADS such as MS, NMOSD, or MOG associated demyelination.[9-11]

MOG is a small component of the myelin exclusively expressed in CNS. Anti-MOG antibodies are a common association in pediatric ADEM. MOG associated demyelination frequently affects the spinal cord and optic nerve and is associated with a relapsing course.[8] Furthermore, younger children may have more severe illness due to immaturity of myelin, leading to secondary injury and permanent axonal loss.

ADEM may be classified retrospectively based on the clinical course and relapses. The subtypes include monophasic ADEM, multiphasic ADEM, acute hemorrhagic leukoencephalitis (AHLE) and ADEM optic neuritis (ADEM-ON).[2-4] Monophasic ADEM refers to a single event without any recurrence or a phenotype of AHLE. The term recurrent ADEM is not used as per recent terminology. A second event with encephalopathy, three months beyond the initial event, is referred to as multiphasic ADEM. More than two episodes suggest a different diagnosis such as MS, depending on the clinicoradiological and serological profile. ADEM-ON includes patients with monophasic or multiphasic ADEM with one or more episodes of optic neuritis and is classically associated with anti-MOG seropositivity.[8] Multifocal hemorrhages and necrosis, along with demyelination, characterize AHLE. This condition has a grave prognosis and is often life-threatening.[3,12] The diagnosis of MS is established after ADEM, if it is followed by another non-ADEM event occurring after three months of the initial event with dissemination in space.

Diagnosis

ADEM is a diagnosis of exclusion. Investigations are warranted to exclude the other causes of encephalopathy. The primary differential diagnoses include infectious meningoencephalitis, intoxication, CNS vasculitis, leukodystrophy, CNS malignancy, metabolic disorders and other disorders that affect the white matter. Brain MRI, cerebrospinal fluid (CSF) studies, serum autoantibodies and oligoclonal bands may help in reaching the diagnosis.

Neuroimaging: A contrast-enhanced MRI of brain with optic nerve cuts and spinal cord is the imaging modality of choice. Several radiological patterns have been described in brain MRI for ADEM (Box 2).[13] Multifocal, large, ill-defined, T_2 hyperintense lesions in cerebral white matter with or without deep gray matter/ brainstem involvement are characteristic neuroimaging findings in ADEM[3] (Fig.1-3). T1 hypointense lesions (black holes, typical of MS) and cortical gray matter lesions are rarely seen. Contrast enhancement is common and ring-like enhancement may also be seen in tumefactive ADEM. Diffusion restriction and hemorrhagic lesions are rare. There might be concurrent optic neuritis or transverse myelitis. The image may resemble other disorders affecting the brain white matter and a careful review of history, and other findings help in the clinical distinction (Fig.4).

CSF studies: They are non- specific and help in ruling out other disorders. CSF should be sent for cell count, protein, sugar, oligoclonal bands, and workup for infective causes. In ADEM, CSF is often unremarkable, but may show lymphocytic pleocytosis (29-85%), elevated proteins (17-48%) and oligoclonal bands (up to 20% of cases).[3]

Box 2. ADEM - MRI patterns[13]

1. Small lesions <5mm
2. Large tumefactive lesions
3. Bithalamic involvement
4. Acute hemorrhagic leukoencephalitis (Weston Hurst Disease)
5. Pseudo leukodystrophic pattern

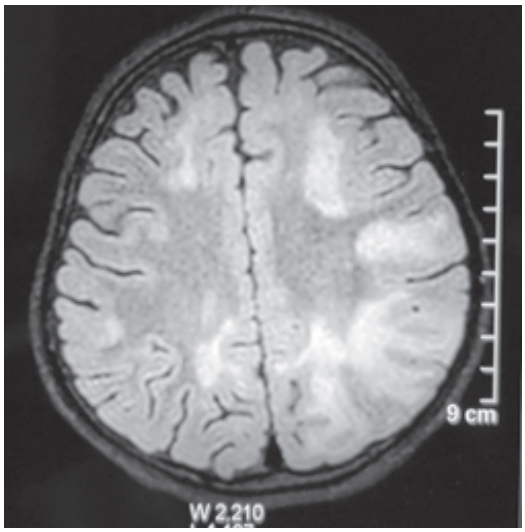

Fig.1. ADEM - MRI brain axial FLAIR image – Well / ill-defined multifocal white matter hyperintensities

Specific serum antibody testing: Anti-MOG antibody and anti-aquaporin 4 antibody (AQP4 -Ab) testing in serum are useful for the diagnosis of MOG associated demyelination and NMOSD. MOG antibody is frequent in childhood ADEM and may be seen in 33- 66% cases.[8,14] They are related to a non-MS relapsing course.[14] Aquaporin-4 antibody positivity is rare in ADEM. Antinuclear antibodies may rarely be seen in childhood ADEM.

Electroencephalogram (EEG): EEG may be done as a part of the workup for encephalopathy to rule out non-convulsive status. In ADEM, it usually reveals non-specific findings such as diffuse or focal slowing and focal spikes.[15]

Histopathology: This may be rarely warranted in cases with diagnostic dilemmas such as those with large tumefactive lesions. The essential purpose is to rule out CNS malignancy or CNS vasculitis in cases with diagnostic uncertainty. Pathologically, perivenous demyelination, along with the presence of inflammatory infiltrate is characteristic of ADEM.[16]

Treatment

The management of ADEM is based on consensus opinions and expert guidelines with evidence from case reports and case series. There are no randomized controlled trials till date to guide the management. The management of ADEM may be divided into three parts: a) supportive, b)specific immunomodulatory therapies and c) rehabilitative measures.

Supportive measures include maintenance of systemic functions (airway protection, seiure control, fluid and electrolyte balance) during the acute illness. Specific immunomodulatory therapies include steroids, immunoglobulins and plasma exchange. The most widely accepted first-line treatment is high-dose corticosteroids.[3,4] Pulse methylprednisolone therapy at a dose of 20-30 mg/kg/day (maximum of 1000 mg/day) for 3-5 days, followed by tapering over 4-6 weeks with oral steroids, remains the treatment of choice. Complete recovery is reported in 50-80% of the cases treated with corticosteroids. If corticosteroids fail, other options include intravenous immunoglobulin (IVIG) and plasmapheresis. Plasma exchange is a well-tolerated procedure that improves outcomes in more than 70% of the patients who fail high-dose steroids.[16] Evidence suggests that earlier the initiation of therapy, better the outcomes.[17] IVIG has also been used for patients non-responsive to pulse steroids.[18] Cyclophosphamide may also be used in fulminant ADEM if steroids, IVIG or plasmapheresis fail.[19]

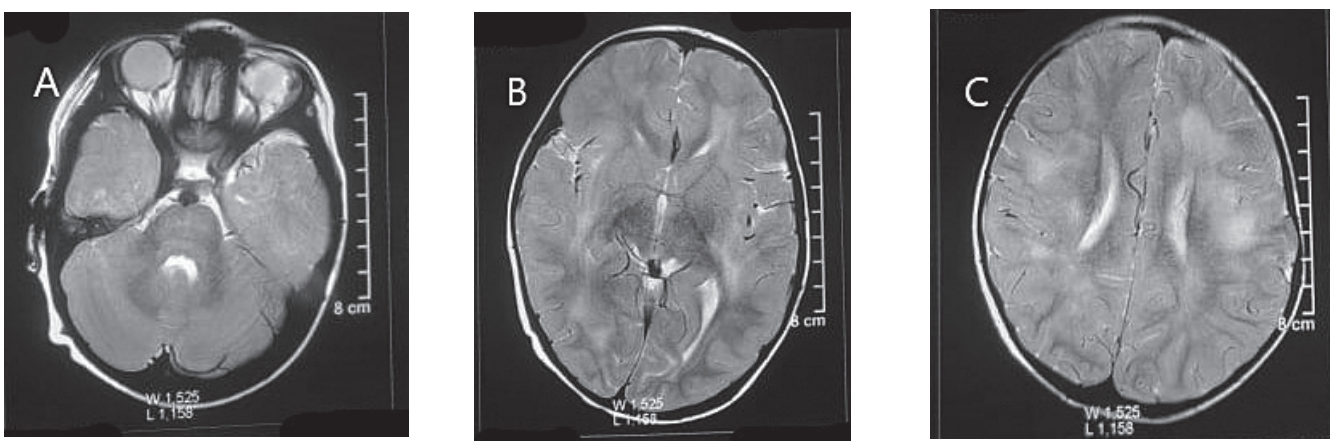

Fig.2. MRI brain axial T2 images - Multifocal hyperintensities in pons (A) and cerebral white matter (B,C).

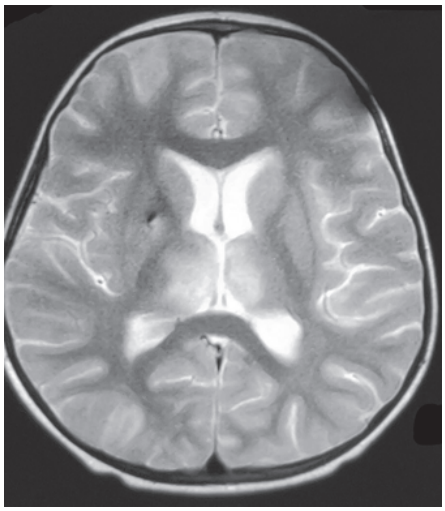

Fig.3. MRI brain axial T2 images - Typical thalamic involvement.

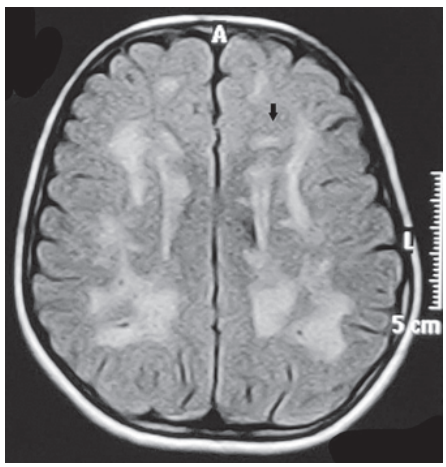

Fig.4. MRI brain axial FLAIR image - Well defined multifocal white matter hyperintensities. Note the linear pericallosal hyperintensities (Black arrow)

Treatment of MOG - associated demyelination: Although MOG-Ab-associated demyelination is usually described to be less severe and has a better outcome compared to AQP4-Ab associated disease, disability can result from incomplete recovery.[8,14] The treatment recommendations for acute management of MOG associated demyelination is similar to that of ADEM and includes intravenous corticosteroids, IVIG and plasma exchange with steroids tapered over 4-6 weeks as the results of the antibody testing may become available by that time.[20] Initiation of maintenance treatment for relapse prevention depends on the likelihood and the number of relapses, the extent of recovery from each event and the severity of the acute event. Rituximab, mycophenolate mofetil, azathioprine and monthly IVIG have been reported to be associated with improvement in the annualized relapse rates (ARR). Regular IVIG (every four weeks) with its added benefit of not inducing immunosuppression, is reported to be associated with maximum improvement in the ARR and Expanded Disability Status Scale (EDSS) scores.[20]

Prognosis

Prognosis following the acute episode of ADEM depends on the recovery after the acute stage and the risk of recurrent demyelination episodes. Prognosis in children is considered to be better than in adults with lower chances of progression to MS. Prognosis of MOG associated demyelination is better with more resolution of clinical and radiological features; however, there is an increased risk of non-MS recurrences.[3]

Points to Remember

- ***ADEM is an inflammatory disorder of the brain, characterized by acute-onset polyfocal neurologic deficits and encephalopathy.***
- ***Fluffy white matter demyelinating lesions are the typical MRI findings.***
- ***ADEM is monophasic, but it may be the first presentation of related inflammatory disorders such as MOG associated demyelination.***
- ***Treatment includes immunomodulation with pulse steroids resulting in a brisk improvement in most children.***
- ***IVIG is initiated if there is no clinical improvement within seven days of completing pulse steroids.***

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CLIPPINGS

The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application.

A novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in China in December 2019. Study was undertaken to evaluate the incubation period of COVID 2019 (Corona virus disease 2019). Pooled analysis of cases confirmed between between 4 January 2020 and 24 February 2020 were analysed. 181 COVID 19 confirmed patients outside Wuhan were studied.

Authors have stated the following. Median incubation period was estimated to be 5.1 days (95% CI, 4.5 to 5.8 days) and 97.5% of those who develop symptoms will do so within 11.5 days (CI, 8.2 to 15.6 days) of infection. Under conservative assumptions, 101 out of every 10 000 cases (99th percentile, 482) will develop symptoms after 14 days of active monitoring or quarantine. The authors concluded that the existing policy of quarantine for 14 days be justified.

Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med 2020; [Epub ahead of print 10 March 2020]. doi: https://doi.org/10.7326/M20-0504.

NEUROLOGY

METABOLIC ENCEPHALOPATHIES

#Sangeetha Yoganathan
****Bidkar Sayli Umakant***

Abstract: *The etiologies of metabolic encephalopathy are often diverse in children. Encephalopathy could result from lack of glucose, vitamin cofactors or oxygen and end organ failure. Inborn errors of metabolism, hypoglycemia, dyselectrolytemia, endocrine disorders and Reye syndrome are the reported causes of metabolic encephalopathies in children and adolescents. The clinical manifestations, biochemical parameters and radiological findings vary according to the etiology. Early diagnosis and management lead to reversal of symptoms and can prevent long-term neurological sequelae.*

Keywords: *Metabolic encephalopathy, Inborn error of metabolism, Osmotic demyelination syndrome, Hepatic encephalopathy, Uremic encephalopathy.*

Encephalopathy refers to altered mental status that includes "disorientation, short-term memory impairment, inattentiveness and abnormal state of arousal".[1] Intracranial or extracranial pathologies that interfere with the cerebral functions would result in encephalopathy. The common causes of encephalopathy are systemic or central nervous system infection, trauma, toxin exposure, metabolic disorders, organ failure, anoxia, endocrine dysfunction, nutritional deficiencies and neoplasms.[1] The term 'metabolic encephalopathy' was coined by Kinnier Wilson.[2] 'Metabolic encephalopathy' refers to a "clinical state of global cerebral dysfunction induced by systemic stress varying in clinical presentation from mild executive dysfunction to deep coma".[2] 'Acute toxic-metabolic encephalopathy' is characterized by altered level of consciousness, behavioural changes with or without seizures. It is suspected when central nervous system infection, inflammation or structural brain disease are excluded.[3] Clinical features, evaluation and management of the major causes of metabolic encephalopathy excluding hypoxic ischemic and toxin / drug induced encephalopathy are discussed here.

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Pathophysiology

A regulation of balance of water, electrolytes and other metabolic substrates is needed to maintain the local milieu of neurons in the presence of adequate blood flow, temperature and pH.[4] The possible mechanisms of cerebral dysfunction in metabolic encephalopathies are cerebral edema, endogenous accumulation of toxic metabolites, vasogenic or cytotoxic edema, dysregulation of neurotransmitter function, disruption of neurotransmission and energy depletion.[2,3]

Causes

The metabolic encephalopathies could result from lack of glucose, oxygen and vitamin cofactors and organ failure such as hepatic or uremic encephalopathy.[5] The metabolic disturbances may be transient or permanent. The causes of metabolic encephalopathies (Box 1) might vary depending upon the age of presentation.

Box 1. Metabolic encephalopathy - Causes

- Electrolyte disturbances: hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, hypophosphatemia, hypomagnesemia, hypermagnesemia
- Inborn errors of metabolism: Organic acidemia, urea cycle disorders, mitochondrial cytopathy, Reye syndrome
- Organ failures: Hepatic encephalopathy, uremic encephalopathy, hypoxic and hypercapnic encephalopathy
- Endocrine causes: Hypoglycemia, diabetic ketoacidosis, adrenal crisis, hypothyroidism, hyperthyroidism
- Nutritional deficiency: Wernicke encephalopathy
- Posterior Reversible Encephalopathy Syndrome (PRES)

Dyselectrolytemia - Related encephalopathy

Electrolyte disturbances such as hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, hypophosphatemia, hypomagnesemia and hypermagnesemia often result in encephalopathy. Clinical symptoms may be directly related to electrolyte disturbances or iatrogenic resulting from an inappropriate correction. The laboratory cut-off values above or below which encephalopathy may occur include sodium less than 125 mmol/L (hyponatremia), sodium more than 160mmol/L (hypernatremia), ionized calcium less than 0.5 mmol/L (hypocalcemia), ionized calcium more than 3 mmol/L (hypercalcemia), phosphorus less than 0.5 mmol/L (hypophosphatemia), magnesium less than 0.5 mmol/L (hypomagnesemia) and magnesium more than 2 mmol/L (hypermagnesemia).[2]

Hyponatremia contributes to hypoosmolar stress that drives water into the intracellular space by osmotic forces thereby resulting in cerebral edema. However, a rapid shift of electrolytes and organic osmolytes occurs from the intracellular space to prevent cerebral edema. Severe hyponatremia attributes to failure of adaptive mechanisms resulting in clinical manifestations. Clinical symptoms include headache, lethargy, seizures, vomiting, behavioral symptoms and coma. Hypernatremia leads to hyperosmolar stress that activates the shift of water and electrolytes out of the intracellular compartment resulting in shrinkage of oligodendroglial cells.[2] Clinical symptoms in these patients are altered sensorium and seizures. Dysregulation of calcium homeostasis affects the neuronal excitability, synaptic transmission and function of various organelles. The precise mechanism of encephalopathy in patients with hypomagnesemia is not clear, though it is postulated to result from an influence on the calcium homeostasis. Neurological manifestations in patients with hypocalcemia, hypercalcemia, hypomagnesemia, hypermagnesemia and hypophosphatemia are cognitive disturbances, psychiatric symptoms, seizures, muscle weakness, cramps, hemiparesis, aphasia, extrapyramidal symptoms and respiratory compromise.[2]

Osmotic demyelination syndrome is a rare cause of encephalopathy in children and adults. It has been reported in patients with rapid correction of hyponatremia, malnutrition, burn injuries, cirrhosis, pituitary surgeries, prolonged use of diuretics, hypophosphatemia and folate deficiency.[6] The underlying pathophysiology is impaired ability of brain cells to respond to sudden osmolality changes with resultant intracellular dehydration, energy depletion and axonal damage.[6] Sites of involvement in osmotic demyelination syndrome are pons and extra pontine sites such as basal ganglia, cerebral cortex, hippocampi, lateral geniculate bodies and white matter. Clinical manifestations include altered sensorium, coma, seizures, memory disturbances, dysphagia, flaccid quadriparesis, mutism, tremor, ataxia, dysarthria, dystonia, horizontal gaze paralysis and parkinsonism.[6,7]

Hypoglycemic encephalopathy

Hypoglycemia is one of the common causes of encephalopathy in infants and children. In symptomatic cases, hypoglycemia is defined as blood sugar less than 50 mg/dL and 60 mg/dL in neonates less than 48 hours and after 48 hours of life respectively.[8] Hypoglycemia may occur due to low birth weight, sepsis, hyperinsulinism, inborn errors of metabolism, growth hormone deficiency, adrenal insufficiency and medications. Clinical symptoms in hypoglycemic patients that result from the activation of sympathetic nervous system are tachycardia, sweating, hypothermia, anxiety and tremors. Neuroglycopenic symptoms in these patients include lethargy, headache, seizures and altered sensorium.[8]

Inborn errors of metabolism (IEM)

IEM may be broadly categorized into 3 groups.[9] Group 1 disorders include amino acidopathies, organic acidemia, porphyria and metal intoxication. In group 1 disorders, proximal to the block in metabolic pathways, the metabolites accumulate resulting in acute or progressive intoxication. Group 2 disorders are those resulting from defects in energy production or utilization. Disorders under this group are mitochondrial energy defects such as pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, fatty acid oxidation defects, ketone body

Box 2. Clinical clues for diagnosis of inherited metabolic disorders in neonates and infants

Neurological

Lethargy, coma, poor sucking, apnea, myoclonic seizures, hypotonia or hypertonia, involuntary movements, hiccups, fast breathing

Gastrointestinal

Hepatosplenomegaly, Cholestatic jaundice

Others

Hypothermia, sepsis-like presentation with no response to antibiotics, abnormal urine odor, dysmorphic features, hydrops fetalis

Table I. Specific diagnostic markers for inherited metabolic disorders in general physical and neurological examination

Features	Metabolic disorders
Microcephaly	Sulfite oxidase deficiency, molybdenum cofactor deficiency, untreated phenylketonuria
Facial dysmorphism	Glutaric aciduria type II, peroxisomal disorders
Sparse hypopigmented hair	Biotinidase deficiency, multiple carboxylase deficiency, vitamin B12 deficiency
Hair shaft abnormalities	Arginosuccinic aciduria, Menkes disease
Alopecia	Biotinidase deficiency, multiple carboxylase deficiency
Hypertrichosis	Mitochondrial complex deficiency
Skin rashes	Biotinidase deficiency, multiple carboxylase deficiency
Fat maldistribution	Congenital disorder of glycosylation
Cyanosis	Methemoglobinemia due to cytochrome b5 reductase deficiency
Petechiae	Ethylmalonic aciduria
Anemia	Vitamin B12 deficiency
Ocular findings - Cherry red spot, retinitis pigmentosa, nystagmus, optic atrophy, supranuclear gaze paralysis, strabismus, oculogyric crisis, lens dislocation	Tay-Sachs disease, Niemann Pick disease, mitochondrial cytopathy, homocystinuria, sulfite oxidase deficiency, Gaucher disease, neurotransmitter defects
Spasticity	Nonketotic hyperglycinemia, sulfite oxidase deficiency, molybdenum cofactor deficiency, multiple carboxylase deficiency
Extrapyramidal signs (dystonia, choreoathetosis, tremors)	Glutaric aciduria, Leigh syndrome, biotin thiamine responsive basal ganglia disease, neurotransmitter defects, homocystinuria
Ataxia	L-2-hydroxyglutaric aciduria, vitamin B12 deficiency, cobalamin disorders, mitochondrial complex deficiency

utilization defects and respiratory chain disorders. Group 3 disorders involve the defects in the synthesis or catabolism of complex molecules such as lysosomal storage disorders, peroxisomal disorders, congenital disorders of glycosylation (CDG) and disorders of cholesterol metabolism. Group 1 and 2 disorders usually manifests with acute encephalopathy. Disorders categorized under group 3 manifest with chronic progressive course and episodic decompensation with intercurrent illness may rarely occur in some of these disorders. Hypoglycemia, dyselectrolytemia, cytotoxic edema and energy failure could possibly attribute to encephalopathy in children with various inborn errors of metabolism.

Clinical manifestations of IEM in neonates are often non-specific. Neonates with IEM usually manifest with poor feeding, lethargy, vomiting, failure to thrive, respiratory distress and coma. Other symptoms include neurological deterioration, seizures, jaundice, cardiac failure or refractory hypoglycemia.[9] A full term neonate with no apparent antenatal or perinatal risk factors presenting with sudden neurological deterioration must be evaluated for IEM. Clinical clues for consideration of IEM in full term neonates and infants are summarized in Box 2.[9]

Disorders that exhibit lethargy and progressive neurological deterioration are maple syrup urine disease

(MSUD), methylmalonic acidemia (MMA), propionic acidemia (PA), isovaleric acidemia (IVA), multiple carboxylase deficiency (MCD) and urea cycle disorders (UCD).[9] Seizures are predominantly observed in pyridoxine dependent epilepsy, biotinidase deficiency, folinic acid responsive seizures and hypomagnesemia. Hepatic failure has been reported in galactosemia, tyrosinemia, fructose intolerance, CDG type 1b and bile acid synthesis defects. Cardiac failure and rhythm disturbances have been observed in neonates with fatty acid oxidation defect (FAOD). Disorders of glycogenolysis, hyperinsulinism and FAOD must be considered in neonates with persistent hypoglycaemia.[9]

IEM must be suspected in children of any age with developmental delay, seizures, consanguinity, positive family history, stroke like episodes, vision deterioration, hearing dysfunction, peripheral neuropathy, extrapyramidal signs, ataxia and neurological worsening with intercurrent illness.[10] The clinical markers for diagnosis of inherited metabolic disorders are summarized in Table I.[10]

Nutritional deficiencies

Children with nutritional deficiencies of vitamins such as thiamine, vitamin B12, folic acid and niacin would manifest with altered level of consciousness, memory disturbances, seizures, ataxia and involuntary movements.

Wernicke encephalopathy results from thiamine deficiency and though common in alcoholic patients, it has been reported in infants born to thiamine deficient mother, children with malignancies on chemotherapy, nephrotic syndrome, gastrointestinal surgeries, prolonged hospitalization, magnesium deficiency and inherited thiamine transporter deficiency.[11] The classical triad described in Wernicke encephalopathy consisting of encephalopathy or memory disturbances, ataxia and ophthalmoplegia are not observed in majority of cases. Other uncommon clinical manifestations in Wernicke encephalopathy are seizures, hallucinations, behavioral disturbances, dyskinesias, coma, hypotension and hypothermia.[11] Thiamine deficiency leads to impaired functioning of transketolase, pyruvate dehydrogenase, alpha ketoglutarate dehydrogenase and branched chain ketoacid dehydrogenase resulting in energy depletion and neuronal injury.

Hepatic encephalopathy (HE)

Hepatic encephalopathy occurs commonly in children with fulminant hepatic failure due to viral hepatitis, drug toxicity or inborn errors of metabolism. HE may be acute or chronic. The acute HE would result from liver cell dysfunction and cerebral edema while chronic HE predominantly results from portosystemic shunting.[2] Hyperammonemia, dyselectrolytemia, generation of aberrant neurotransmitter-like molecules, manganese deposition in brain and production of abnormal ligands could explain the neurological symptoms in children with HE.[12,13] The precipitating factors of HE are infection, variceal bleeding, constipation, dehydration, dyselectrolytemia, hypoglycemia, excessive intake of dietary protein, use of sedative drugs and renal failure.[14] There are four types of HE namely type A associated with acute liver failure, type B associated with portosystemic bypass, type C associated with cirrhosis and type D associated with urea cycle disorders.[14] Common IEM responsible for liver failure are tyrosinemia, galactosemia, urea cycle disorder and neonatal hemochromatosis. The clinical stages of HE are summarized in Table II.[15, 16]

Table II. West Haven grading of hepatic encephalopathy[15,16]

Grade	Clinical features
1	Lack of awareness Decreased attention span Impaired calculation Euphoria or anxiety
2	Lethargy or apathy Disorientation of time or place Personality changes Inappropriate behavior Impaired calculation
3	Hypersomnolence Disorientation Stupor
4	Coma

Reye syndrome

Reye syndrome was first described by R.D.K Reye in 1963.[17] It is an acute non-inflammatory encephalopathy that typically manifests with vomiting, lethargy and progression to coma.[17] The criteria to be fulfilled for the diagnosis of Reye syndrome is given Box 3.[18]

Reye syndrome may be precipitated by viral or bacterial pathogens such as influenza virus, varicella zoster virus, coxsackie virus, parainfluenza virus, adenovirus, Epstein-Barr virus, hepatitis virus, chlamydia, bordetella, mycoplasma and shigella. Ingestion of salicylates has also been associated with the occurrence of Reye syndrome. These bacterial / viral pathogens and aspirin appear to cause

Box 3. Reye syndrome – Diagnostic criteria[18]

"Acute noninflammatory encephalopathy that is documented clinically by a) an alteration in consciousness and, if available b) a record of cerebrospinal fluid (CSF) containing less than or equal to 8 leukocytes/cu.mm or a histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation.

Hepatopathy documented by either a) a liver biopsy or an autopsy considered to be diagnostic of Reye syndrome or b) a threefold or greater increase in the levels of the serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) or serum ammonia. No more reasonable explanation for the cerebral and hepatic abnormalities."[18]

Box 4. Clinical stages of Reye syndrome[19]

- Stage 0- Alert, wakeful
- Stage I- Lethargy, drowsy
- Stage II- Delirious, combative
- Stage III- Unarousable, decorticate posturing
- Stage IV- Unarousable, decerebrate posturing
- Stage V- Unarousable, flaccid paralysis, areflexia, dilated and fixed pupils

hepatic mitochondrial injury thereby leading to inhibition of fatty acid oxidation metabolism. Hyperammonemia, hypoglycemia, coagulopathy, cerebral edema and hypoxia are the important determinants of clinical severity. The clinical stages of Reye syndrome may be categorized as shown in Box 4.[19]

Uremic encephalopathy

Children with acute or chronic renal failure may develop uremic encephalopathy with a progressive decline in the estimated glomerular filtration rate. The etiologies for acute or chronic renal failure in children are often diverse. Clinical features of uremic encephalopathy are anorexia, drowsiness, restlessness, poor attention span, cognitive disturbances, bizarre behavior, emotional instability, seizures, stupor and coma.[20]

Involvement of cranial nerves, hyperreflexia, asterixis and focal motor deficits may occur in these patients. The causes of CNS injury in uremic patients are accumulation of uremic metabolites, guanidino compounds and cystatin C, hypertension, dyselectrolytemia, secondary hyperparathyroidism, thiamine deficiency, graft rejection, hyperhomocystinemia, oxidative stress, chronic inflammation, aluminium-related encephalopathy and dialysis disequilibrium syndrome.[21]

Pulmonary encephalopathy

Pulmonary encephalopathy is caused by hypercapnia or hypoxemia due to respiratory insufficiency of varied etiology. Hypercapnia results in encephalopathy due to CSF acidosis, cerebral vasodilatation and impaired neuronal excitability. Clinical manifestations are headache, agitation, poor attention, drowsiness, stupor and coma.[2]

Posterior reversible encephalopathy syndrome (PRES)

PRES was first described in 1996 by Hinchey et al.[22] Other terminologies that are used to describe PRES are reversible posterior leukoencephalopathy, reversible posterior cerebral edema, reversible occipitoparietal encephalopathy and hypertensive encephalopathy. PRES occurs in children and adults with uncontrolled hypertension of varied etiology, use of immunosuppressive drugs and antiretroviral drugs, blood transfusion, hypercalcemia, eclampsia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, von Hippel Lindau disease and exposure to contrast media.[23] Though the pathophysiology underlying PRES remains debatable, the possible mechanisms are impaired cerebrovascular autoregulation, endothelial damage and vasogenic edema.[23] PRES is a clinicoradiological entity and the reported symptoms in these patients include headache, vomiting, seizures, lethargy, somnolence, stupor, coma, visual disturbances and focal motor deficits.[2]

Endocrine dysfunction-related encephalopathy

Endocrine dysfunction manifests with varied neurological manifestations that ranges from headache, myopathy to encephalopathy and coma. Diabetic ketoacidosis, hyperglycemic hyperosmoloar coma, adrenal crisis, hypothyroid coma, hyperthyroid storm and Hashimoto's encephalopathy are the common causes of endocrine dysfunction-related encephalopathies.[24]

a) Hyperglycemic encephalopathy occurs in children and adolescents with diabetes mellitus due to diabetic ketoacidosis (DKA) or nonketotic hyperosmolar hyperglycemia. DKA occurs more commonly in type-1 diabetes mellitus, often precipitated by starvation, exercise

and infection. In the absence of insulin, triglycerides in the liver are broken down to fatty acids and glycerol and the glycerol is again converted in to glucose. However, the glucose thus formed cannot be utilized by the peripheral tissues due the lack of insulin leading on to a rise in the production of ketone bodies. Hyperglycemia, glucosuria, high anion gap metabolic acidosis, hypokalemia and ketosis are the biochemical markers of DKA. Clinical manifestations in children with DKA are lethargy, abdominal pain, vomiting, polyuria, polydipsia, dehydration, tachypnea and altered sensorium.[25]

b) Hyperosmolar hyperglycemic syndrome (HHS) occurs more commonly in type-2 diabetes mellitus, often precipitated by infection. In HHS, despite hyperglycemia, the peripheral tissues are unable to utilize the glucose and hence, counter regulatory hormones are released that raises the blood sugar level and serum osmolarity. Since the insulin levels are not decreased in type-2 diabetes, lipolysis and ketogenesis are inhibited. Children with HHS manifest with fever, lethargy, tachypnea, tachycardia, dehydration, focal neurological deficits and altered sensorium.[26]

c) Hypothyroid coma is extremely rare in children. These children usually manifest with lethargy, bradycardia, hypothermia, dyspnea and seizures. In children with hypothyroidism, factors that attribute to clinical symptomatology are hyponatremia, hypothermia, hypoventilation and hypoxia. Hashimoto's encephalopathy refers to an immune-mediated neurological disorder with varied clinical symptoms such as seizures, movement disorders, psychiatric symptoms and coma. Though the exact pathophysiology is not clear, it is believed to result from an underlying immune-mediated pathogenic process. Anti-thyroglobulin and anti-microsomal antibodies are detected in these patients despite the euthyroid state.[27] The treatment modalities include high dose steroids, plasmapheresis and intravenous immunoglobulins.[27,28]

d) Patients with hyperthyroidism rarely manifest with thyroid storm following surgery, trauma or infection. These patients exhibit tremors, seizures, involuntary movements and coma.

e) Adrenal crisis is usually precipitated by dehydration, infection, trauma in children with pre-existing adrenal insufficiency and also following abrupt withdrawal of steroid. These patients manifest with lethargy, vomiting, hypotension, shock, confusion and coma.[29,30]

Clinical spectrum

Though the signs of global cerebral dysfunction predominate in metabolic encephalopathies, a careful clinical examination to look for neuropsychological signs

Table III. Neuroimaging findings in metabolic encephalopathies of different etiologies

Etiology	MRI findings
Osmotic demyelination syndrome	Central pontine myelinolysis- trident-shaped hyperintensity in central pons Extrapontine myelinolysis-T2 hyperintensity involving caudate, putamen and other sites of involvement are cerebral white matter and cerebellum
Wernicke encephalopathy	Symmetric signal changes in bilateral thalami, mammillary bodies, hypothalamus, tectal plate, cranial nerve nuclei, dentate nuclei, periaqueductal grey matter and cerebellar vermis
Posterior reversible encephalopathy syndrome	Vasogenic edema in the subcortical white matter of parietal and occipital lobes and rarely cortex. Other sites are subcortical white matter in frontal region, basal ganglia, thalamus and cerebellum
Uremic encephalopathy	Lentiform fork sign involving basal ganglia on MRI
Hepatic encephalopathy	T1 hyperintensity involving bilateral globus pallidi MRS show increased glutamine/glutamate peak and decreased myoinositol and choline peaks
Reye syndrome	Signal changes in bilateral thalami, brainstem, cerebellar white matter, subcortical white matter and cerebral cortex

Table IV. Neuroimaging findings in children with inherited metabolic disorders

Imaging findings	Metabolic disorder
Intracranial calcification on CT brain	Dihydropteridine reductase deficiency MELAS Kearns Sayre syndrome Congenital lactic acidosis Respiratory chain disorders
White matter signal changes on T2Weighted images	Glutaric aciduria type I L-2-hydroxyglutaric aciduria Menkes disease Sulfite oxidase deficiency Molybdenum cofactor deficiency PKU MSUD Peroxisomal disorders Mitochondrial complex deficiency
Basal ganglia or brainstem signal changes	Biotin thiamine responsive basal ganglia disease Leigh syndrome L-2-hydroxyglutaric aciduria Methylmalonic aciduria Mitochondrial complex deficiency Wernicke encephalopathy Osmotic demyelination syndrome
Dentate nuclei hyperintensity	L-2-hydroxyglutaric aciduria Mitochondrial encephalopathy Succinate semialdehyde dehydrogenase deficiency
MRS findings	Prominent NAA peak- Canavan disease Prominent lactate peak- mitochondrial cytopathies Absent creatine peak- cerebral creatine deficiency syndromes

MELAS- Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes, NAA - N acetylaspartate

and focal neurological deficits is mandatory. The spectrum of neuropsychological changes in metabolic encephalopathies include disturbances of consciousness such as hypersomnolence, decreased arousal, stupor and coma, memory disturbances, thought and perception problems and increased or decreased psychomotor activity. Autonomic disturbances may also occur in these patients. Global brainstem signs such as orofacial automatisms, pathological reflexes, asterixis, myoclonus, tremor, decerebrate and decorticate posturing can be seen. Focal cerebral and brainstem signs that may occur in patients with metabolic encephalopathies are aphasia, hemiparesis, vision disturbances, dysarthria, nystagmus, gaze deviation, pupillary abnormalities, hemisensory loss, changes in tone and deep tendon reflexes and ataxia.[31]

Laboratory diagnosis

In children with suspected metabolic encephalopathies, the etiology could be established by meticulous history taking, clinical examination, arterial blood gas analysis, blood biochemistry tests, neuroimaging and electroencephalography (EEG).[32] A high anion gap metabolic acidosis will be detected in children with diabetic ketoacidosis and lactic acidosis. In those children with documented ketoacidosis, estimate the blood sugar, blood ammonia and lactate to identify an underlying IEM. Respiratory acidosis will be detected in children with pulmonary encephalopathy due to hypercarbia. Neuroimaging forms an important diagnostic tool in establishing the etiology of metabolic encephalopathies in

children. The summary of neuroimaging findings in children with metabolic encephalopathies of varied etiology and suspected inborn errors of metabolism are summarized in Table III and IV.[10,11,33-38]

Freshly voided urine samples must be collected in infants and children with suspected metabolic encephalopathies. Urine samples have to be collected before treatment and while on treatment. These samples have to be stored at -20° C and urinary samples are to be analyzed for odour, P^H, sulfite excretion, electrolytes, ketones, amino acid and ketoacids.[9] Urinary organic acids are analyzed by gas chromatography-mass spectrometry (GCMS). Plasma, dried blood spot on filter paper and whole blood are collected and stored in appropriate vials.

Neuroimaging plays a vital role in identifying the etiology of metabolic encephalopathies. Other laboratory tests that needs to be considered in children with metabolic encephalopathies are shown in Table V.[9, 39-41]

Treatment

The management of metabolic encephalopathies can be categorized as general and specific measures.

1. General measures in children presenting with metabolic encephalopathies involve the management of airway, breathing and circulation. Maintain euglycemia, correct dyselectrolytemia if identified and supplement thiamine or other vitamin cofactors in cases with Wernicke encephalopathy or other inborn errors of metabolism. Antiepileptic medications must be chosen appropriately to achieve seizure freedom. Raised intracranial pressure if identified must be managed appropriately using standard protocols. Strict control of hypertension and elimination of precipitating factors are recommended in management of children with PRES.

2. Specific measures and organ support

a) The management of hepatic encephalopathy involves maintenance of fluid and electrolyte balance and euglycemia. Other measures that target to decrease the blood ammonia levels in children with hepatic encephalopathy are protein restricted diet; use of antibiotics such as ampicillin and metronidazole to reduce gut bacterial colonization and use of sodium benzoate and phenyl acetate.[12]

Table V. Laboratory evaluation of children with metabolic encephalopathies

Biological samples	Biochemical tests
Blood	Basic tests: Complete blood count, ESR and CRP fasting blood sugar, sodium, potassium, calcium, phosphorus, magnesium, arterial blood gas, lipid profile, uric acid, liver function test, prothrombin time, creatine kinase, Nutrition and metabolic tests: ammonia, lactate, amino acids, acyl carnitine profile, homocysteine, vitamin B12, prolactin, VLCFA, isoelectric focusing for transferrins, tandem mass spectrometry, free fatty acids, urine porphobilinogen, urine delta-aminolevulinic acid, Molecular studies Endocrine tests: Thyroid function tests and thyroid antibodies, serum cortisol Toxin assay: From gastric aspirate, blood and urine
CSF	Cell count, glucose, protein, lactate, amino acid, neurotransmitters, bacterial culture, PCR for viruses
Ultrasound abdomen, ECG, Echocardiography	To look for hepatic and cardiac involvement
EEG	To identify background activity, focal slowing, epileptiform discharges, triphasic waves, PLEDS and burst suppression pattern Triphasic waves in hepatic encephalopathy FIRDA inhyperglycemia, hypoglycemia and hyponatremia

ESR- erythrocyte sedimentation rate, CRP- C-reactive protein, VLCFA- Very long chain fatty acid, CSF- Cerebrospinal fluid, PCR- Polymerase Chain Reaction, ECG- Electrocardiography, EEG- Electroencephalography, PLEDS- Periodic Lateralized Epileptiform Discharges, FIRDA- Frontal intermittent rhythmic delta activity

b) Hemodialysis or peritoneal dialysis may be useful in selected cases. Dialysis must be considered in children with uremic encephalopathy and these patients also require an emergent management of associated dyselectrolytemia.

c) Therapies in children with Reye syndrome are focused to maintain the cerebral perfusion pressure and also includes supportive measures such 10% dextrose infusion, raised ICP management and correction of hyperammonemia to minimize the neurological sequelae.[42]

d) Adrenal crisis is managed by volume expansion with intravenous fluids and correction of hyponatremia and hypoglycemia. Stress dose of hydrocortisone (100 mg/m^2/day) must be administered as infusion or bolus in the first 24 hours and may be gradually tapered to oral maintenance doses. Treatment of infection is also crucial in patients with adrenal crisis.[30]

e) Children with diabetic ketoacidosis are managed with appropriate intravenous fluids, insulin infusion and correction of dyselectrolytemia. In contrast to DKA, fluid replacement is the key step in management of hyperosmolar hyperglycemic syndrome while insulin infusion is not crucial.[43]

Points to Remember

- ***Metabolic encephalopathy should be suspected in any child with altered consciousness after excluding CNS infection, structural disorders, toxin ingestion and trauma.***
- ***Organ or system failure like hepatic encephalopathy, hypoxia, dyselectrolytemia and endocrine dysfunction are responsible for metabolic encephalopathy.***
- ***Underlying etiologies are diverse which can be narrowed down by recognizing the clinical clues.***
- ***Management includes acute stabilization and specific measures based on etiology including organ support.***

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NEUROLOGY

ACUTE FLACCID PARALYSIS BEYOND POLIO- A CASE BASED APPROACH

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Abstract: *Acute flaccid paralysis is a complex clinical syndrome that requires immediate and careful evaluation for making a diagnoses. Each case of acute flaccid paralysis is an emergency from both clinical as well as public health perspective. The precise knowledge of the etiology, underlying pathophysiology and concurrent changes have profound implications in the treatment and prognosis. With the eradication of polio, Gullian Barrie Syndrome has become the major acute flaccid paralysis. Seasonal occurrence of Gullain Barrie Syndrome with spurt of viral fever is also seen. However, the clinical features of polio must be taught to the younger residents since imported or vaccine associated polio can still occur. Better usage of Magnetiic resonance imaging scanning will help in establishing the diagnosis. Acute management of such patient with acute flaccid paralysis due to different causes in intensive care unit has become a necessity. Based on severity IVIg for Gullain Barrie Syndrome and Methyl prednisolone for transverse myelitis are now accepted protocols. We are still in the process of consolidating the eradication of polio by the endgame strategy from 2019-2023.*

Keywords: *Acute flaccid paralysis, Guillain-Barre Syndrome, Lower motor neuron localization, Transverse myelitis*

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Acute flaccid paralysis (AFP) is an acute onset flaccid weakness, less than 4 weeks, reaching its maximum severity in days to weeks. Some of the causes of AFP are Guillain-Barre syndrome (GBS), poliomyelitis, transverse myelitis (TM), traumatic neuritis and post diphtheritic neuropathy. Continued surveillance of AFP is required to completely eradicate poliomyelitis. A case for surveillance of AFP is defined as any case of AFP in children <15 year old, or any paralytic illness at any age when polio is suspected. Many reviews are available on AFP and this article outlines a case based approach, to highlight the varied presentation.

Etiologies of AFP[1]

It is easier to analyse the cause based on anatomic location

- Brain stem: GBS with cranial nerve involvement, brain stem encephalitis and stroke
- Spinal cord: Acute transverse myelitis, acute myelopathy due to spinal cord compression (abscess, space occupying lesion), anterior spinal artery syndrome.
- Anterior horn cells: Poliomyelitis, non-polio enteroviruses.
- Nerve root (radiculopathy): Guillain Barre syndrome.
- Peripheral nerve: Guillain Barre syndrome, toxic neuropathies (diphtheria, tick bite paralysis, lead, arsenic poisoning) traumatic neuritis, acute intermittent porphyria, critical illness neuropathy.
- Neuromuscular junction: Myasthenia gravis, botulism, snake bite, organophosphorus poisoning.
- Muscle: Polymyositis, trichinosis, hypokalemia, hypophosphatemia.

Clinical approach

Usually sudden occurrence of flaccid weakness denotes lower motor neuron (LMN) weakness. However, upper motor neuron (UMN) weakness of sudden onset also can have flaccid weakness in the initial stages due to the neuronal shock state. Following a systematic clinical approach based on the distribution and progression of weakness, associated sensory involvement, fever etc. will

help in differentiating various conditions. Gradual onset of weakness and chronic conditions like spinal muscular atrophy are not included here.

Localization based on clinical signs (Table I)

First step in the diagnosis is localizing the lesion.

LMN: Flaccid weakness with absent reflex is in favor of LMN. After ascertaining that the motor weakness is due to LMN, exact site of lesion like anterior horn cell, root, nerve, myoneural junction or muscle is determined by verifying the presence or absence of cranial nerve lesions, bladder involvement, tendon reflexes and sensory involvement. Associated clinical features may give a clue to the etiological diagnosis (Table II).[2]

Anterior horn cell disorders

Case history

Seven year old child was seen with history of fever, severe myalgia, back pain and weakness of abduction of right shoulder. Examination revealed meningeal signs, mild bulbar weakness, normal sensory and sparing of bladder and bowel. CSF showed lymphocytic pleocytosis. NCV/EMG suggested anterior horn cell disease. Serology revealed enterovirus (type was not determined) on follow up flail shoulder with severe wasting of deltoid was persisting.

Comment: Child had a poliomyelitis like presentation, without isolation of any type of polio virus, but due to another enterovirus.

Febrile illness, rapidly progressive asymmetric weakness, preserved sensory function, severe myalgia and residual paralysis after 60 days are features of polio like illness.[3,4] Enterovirus 71, Coxsackie, Echo and West Nile viruses are the non polio viruses reported.[5] After the eradication of polio, new viral infections can present as polio like illnesses. As oral polio vaccine is still used for vaccination, there is a very remote risk of vaccine derived poliomyelitis.

Radicles and peripheral nerve

Case history

Ten year old boy was admitted with weakness of lower limb of five days and upper limb of two days duration. It started as knee buckling, difficulty climbing stairs and getting up from sitting position. He had difficulty sipping water from a glass but was able to wear slippers and hold the objects in hand. On 3rd day as he developed difficulty raising arm above shoulder and respiratory muscle weakness. He had pain in the legs but no sensory loss. There was no difficulty in urination. He had an upper respiratory tract infection 2 weeks ago.

Comment: Pure proximal motor limb weakness with bifacial palsy and presence of respiratory muscle weakness is diagnostic of GBS. GBS presenting as painful limping may be confused as synovitis. Absent reflexes points towards GBS. Bifacial palsy can be missed as there is no facial deviation due to the symmetric weakness. Difficulty puckering the lips or sipping, incomplete burying of eye lashes on tight eye closure are the clues.

Guillain Barre syndrome (GBS)

It is a progressive, near symmetrical weakness occurring in more than one limb with areflexia (Modified Asbury's criteria) (Box 1). The common subtypes are acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), Miller Fisher syndrome (MFS) and polyneuritis cranialis. The rare variants of GBS are acute pan-dysautonomia, acute sensory

Table I. Localization based on clinical signs

Anatomical level	Clinical signs
Brain stem	Altered consciousness, cranial nerve paralysis, Upper motor neuron (UMN) lesion signs
Spinal cord	Bladder involvement, UMN lesion signs (below the level of lesion), plantar extensor
Anterior horn cells	Lower motor neuron (LMN) type weakness, areflexia
Nerve root	Lower motor neuron weakness, areflexia. No sensory loss
Peripheral nerve	Sensory loss, glove and stocking sensory involvement, loss of ankle reflex
Neuromuscular junction	Diurnal variation, fluctuating weakness
Muscle	LMN weakness but reflexes preserved

Table II. Clues to diagnosis

Features	Diagnosis
Fever	Polio, Lyme disease
Myalgia or sensory symptoms	GBS
Recent exanthem	Lyme disease
Patch over tonsillar area, bull neck	Diphtheria
Trauma/IM injection	Traumatic neuropathy
Abdominal pain	Porphyria, lead poisoning
Exposure to chemicals	Arsenic, lead poisoning
Tick bite	Tick paralysis
Ptosis, respiratory paralysis	Snake bite, botulism
Dermatological manifestations - Edema, Gottron's papules	Dermatomyositis
Recurrent flaccid paralysis	Periodic paralysis - channelopathies
Acute paralysis occurring in an ICU patient	Critical illness neuropathy

ataxia with or without ophthalmoplegia**,** pharyngeal-cervical-brachial weakness and facial diplegia with paresthesias. Preceding infections associated with GBS include Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus, mycoplasma pneumonia and HIV.[6]

MFS is characterized by ataxia, ophthalmoplegia and areflexia without weakness. Anti-ganglioside GQ1B antibodies are commonly detected in MFS. Brain stem encephalitis also can have a similar presentation with ataxia and ophthalmoplegia. However somnolence will be a distinguishing feature.

Electrophysiological abnormalities of GBS: Nerve conduction studies (NCV) are helpful in confirming the diagnosis. The first changes in AIDP are delayed or absent F and H responses, reflecting proximal demyelination. Prolonged distal latencies, decreased conduction velocities along with evidence of segmental demyelination, (conduction block and temporal dispersion) are other changes present in 50% of patients by 2 weeks and in 85% by 3 weeks.

Box 1. Guillain Barre syndrome - Diagnostic criteria

- Presence of progressive weakness and areflexia
- Symmetrical involvement
- Mild sensory involvement, cranial nerve involvement, at least partial recovery
- Autonomic dysfunction
- Absence of fever
- Cerebrospinal fluid features supporting the diagnosis are an increase in protein beyond the first week, cell count < 10 (albumin-cytological dissociation)

The features raising doubt on the diagnosis of GBS are persistent asymmetry of weakness, presence of a sensory level, bowel/bladder involvement at onset and a prominent CSF pleocytosis.

Conditions that may have a presentation like GBS include neuropathy associated with HIV, Diphtheria, Lyme disease, porphyria and critical illness; polyneuropathy/ myopathy and vasculitis syndromes.

Acute transverse myelitis (TM) (Box 2)

It presents as sudden limb weakness, bowel-bladder and sensory disturbances and commonly occurs in toddlers and adolescents.

Postinfectious TM: Preceded by viral or bacterial infection. Viruses implicated are enteroviruses, coronavirus, coxsackie, cytomegalovirus, Epstein-Barr, herpes-simplex, hepatitis A, HIV, influenza, measles, rubella, varicella, and West Nile virus. Bacteriae include mycoplasma pneumoniae, rickettsia, beta hemolytic Streptococcus, borrelia, chlamydia and leptospira.

Box 2. TM - Criteria for diagnosis

- Sensory, motor, or autonomic dysfunction attributable to the spinal cord
- Absence of compressive cord lesion
- Bilateral symptoms and signs
- Definite sensory level
- Spinal T2 MRI- hyperintense signals
- Evidence of inflammation
- CSF pleocytosis, elevated IgG index, or gadolinium enhancement on MRI
- Progression to nadir between 4 hours and 21 days[6,7]

Post-vaccinal TM: May follow immunization for rabies, hepatitis B, influenza, Japanese encephalitis, diphtheria/ pertussis/tetanus, measles, mumps, rubella, pneumococcus, polio, smallpox and varicella.

Acute flaccid paralysis with sensory level is a feature of TM. In children, mild sensory symptom like hyperaesthetic sites may be present which helps for localization. If legs are affected the sensory level is commonly at umbilicus or at the level of nipple. If the arms are weak, look for sensory level at cervical region. Bowel and bladder involvement cause constipation and urinary retention. Respiratory failure (intercostals or diaphragmatic weakness) may occur with higher level lesions.

Variants of TM: Identifying TM variants will help in etiological diagnoses and thus treatment and prognoses

1. Longitudinally extensive TM (LETM) - Lesion in >3 spinal segments associated with bilateral optic neuritis = neuromyelitis optica spectrum disorder.
2. Acute flaccid myelitis (AFM) - Like poliomyelitis they have segmental LMN (AHC) and additional UMN lesion in the setting of other viral infections - e.g. enterovirus D68. These patients may recover with residual wasting and weakness
3. Acute partial TM - Asymmetric extending one to two spinal segments.
4. Acute complete TM - Symmetric, complete or near complete manifestations

An important differential of TM is acute spinal cord infarct due to anterior spinal artery occlusion.[6] Compressive myelopathy can present as acute syndrome. Both intramedullary and extramedullary compression like neuroblastoma can present acutely.

Case report

13 year old boy presented with episodes of vomiting, retching, hiccup and rapidly progressive weakness of both lower limbs and left upper limb. He had urinary retention and was frequently slipping to sleep. Sensory level was localized to T2 and tendon reflexes were sluggish with extensor plantar.

His MRI showed T2FLAIR hyperintensities involving both grey and white matter of cerebral hemispheres and a large lesion on the floor of 4th ventricle. He had an extensive hyperintensity of spinal cord extending from C5 -T1. His myelin oligodendrocyte glycoprotein (MOG) antibody titer was positive. This case exemplifies transverse myelitis with area postrema syndrome. An aquaporin 4 negative MOG positive neuromyelitis optica spectrum disorders (NMOSD).

Comment: Though bladder symptoms, sensory level localize the lesion to spinal cord, retching, vomiting and hiccup point to area postrema involvement (The area postrema is a highly vascular paired structure in the medulla oblongata in the brainstem, in the caudal fourth ventricular floor. It is a critical homeostatic integration center for humoral and neural signals by means of its function as a chemoreceptor trigger zone for vomiting in response to emetic drugs).

Traumatic neuropathy (TN)

Traumatic injury to peripheral nerves presents as focal AFP. It includes injury to plexus, roots or peripheral nerves. Nerve injuries can result from penetrating trauma (injections, falling on sharp objects), entrapment or from traction injuries. Focal weakness is attributable to a single or multiple nerve distribution.

It is asymmetric. History of trauma is present near a nerve or site of predilection. The common cause is an injection to gluteal or deltoid region. Commonly affected nerves are common peroneal / sciatic (foot drop) or radial (wrist drop). The knowledge of anatomy of nerve will help in identifying the specific nerve. The diagnosis is confirmed by nerve conduction studies. The prognosis depends on severity of injury. Persistent, severe and refractory neuropathic pain may be present along with weakness.

Muscle

Case report

Eleven year old girl was admitted with 2 weeks history of painful weakness of upper and lower limbs. No sensory signs. Examination showed grade 3 power in proximal and grade 4 in distal muscles. She had neck flexor weakness. Knee jerk and biceps jerk were very sluggish with easily

Table III. Differential diagnosis of AFP

Features	Poliomyelitis	GBS	Transverse myelitis	Traumatic neuritis
Progression to full paralysis	24-48 hrs	Hours to days	Hours to 4 days	Hours to days
Fever onset	High, always present at onset of paralysis	No	Present before paralysis	No
Distributing of weakness	Asymmetrical, patchy	Symmetrical, distal Ascending	Symmetrical lower limbs	Confined to nerve distribution
Muscle tone	Diminished	Diminished	Diminished in lower limbs	Diminished
Deep Tendon reflexes	Decreased or absent	Absent	Absent early, hyperreflexia late	Decreased or absent
Plantar reflex	Absent/Flexor	Absent/Flexor	Extensor	Absent/Flexor
Sensation	Severe myalgia or backache no sensory changes	Cramps, tingling, hypo anesthesia of palms and soles	Anesthesia of lower limbs with sensory level	Pain in the gluteal region
Cranial nerves	Only in the presence of bulbar or bulbo-spinal involvement	Often present, affecting nerves VII, IX, X, XI, XII	Absent	Absent
Respiratory insufficiency	Only in the presence of bulbar and bulbo-spinal involvement	In severe cases	Sometimes	Absent
CSFexamination	Cell count raised, protein normal or slightly increased protein	<10 leukocytes, high protein	Cell count: Normal/ moderate lymphocytic pleocytosis Protein:Normal/ slightly elevated	Cell count: Normal Protein: Normal
Bladder dysfunction	Absent	Transient	Present	Never
EMG at 3 week	Abnormal	Normal	Normal	May be abnormal
NCV at 3 week	Normal	Abnormal demyelination /axonal	Normal	Abnormal
Sequelae at 3 months	Severe, asymmetrical atrophy	Symmetrical atrophy of distal muscle	Diplegia, atrophy after years,	Moderate atrophy of affected limb

elicitable ankle jerk. Skin examination showed typical features of dermatomyositis. CPK was found be raised.

Comment: Pure motor syndrome with proximal involvement (grade 3 power, sluggish knee and biceps jerk) and high CPK indicated muscle disease. Acute onset and neck weakness suggested polymyositis and skin manifestations clinched the diagnosis of dermatomyositis.

Polymyositis-dermatomyositis

AFP can be due to myositis also. Polymyositis-dermatomyositis can be suspected when there is a symmetric proximal muscle weakness without sensory symptoms or signs and with preserved reflexes, neck muscle weakness, muscle pain and raised CPK**.** Acute myositis following viral infection also are not

uncommon. Temporal relation with viral illness, high CPK and rapid improvement are the features. Some children may require short course of steroid.

Case report

Four year old boy developed weakness of all four limbs and shallow breathing following a diarrheal illness. He required respiratory support for a brief period. Abdominal distension and poor bowel sounds were present. Serum potassium was very low and ECG showed depression of the ST segment, flat T wave with U wave. Consciousness was preserved but tendon reflexes were absent. Weakness rapidly improved with correction of hypokalemia.

Comment: Syndrome of hypokalaemic paralysis represents a heterogenous group of disorders characterised clinically by hypokalaemia and acute pure motor weakness. Sporadic cases are associated with, renal disorders, endocrinopathies and gastrointestinal potassium losses. In adolescents hypokalemic periodic paralysis also can be a possibility.

Neuromuscular junction disorders

Case report

Girl aged nine years was admitted in ICU with rapidly worsening limb weakness and severe respiratory paralysis who required ventilation for 5 days. This happened after a bout of urinary tract infection, which was treated with ciprofloxacin. History of ptosis for 2 weeks occurring in evening hours gave the diagnosis of myasthenic crisis. Rapid deterioration was due to the usage of ciprofloxacin. She improved with IVIg and neostigmine treatment. Acetylcholine receptor (AChR) antibody was positive.

Comment: Usage of certain drugs can worsen treated as well as naïve myasthenia gravis and can present as AFP. Fluctuating weakness, simultaneous ocular and facial muscle involvement and response to neostigmine are the diagnostic pointers. Bite marks and children playing in dark, may suggest snake envenomation. Anti-snake venom and neostigmine will be life saving.

The important features of common causes of AFP are given in Table III.

Investigations

According to AFP surveillance, two stool samples must be collected 24 to 48 hours apart in the first 14 days following the onset of paralysis and to be sent to the accredited lab after following the surveillance protocol for polio or related viral isolation (Fig.1). For diagnosis of other disorders investigations such as blood counts, ESR, peripheral smear, electrolytes (Ca,Mg,K) and CPK. Electrophysiological studies, NCV and EMG are done to evaluate types of GBS, myasthenia, muscle and nerve disorders. MRI of spinal cord and brain for distinguishing various demyelinative disorders.

CSF analysis

Raised CSF cell count is seen in transverse myelitis and infective myelitis viz. polio or enteroviral myelitis, varicella or herpes myelitis and rabies. Albumino-cytological dissociation (increased CSF protein with normal cell count) is seen commonly in GBS but rarely in post-diphtheritic polyneuropathy, transverse myelitis and Froin's syndrome (coexistence of xanthochromia, high protein level and marked coagulation of cerebrospinal fluid due to obstruction of CSF flow may indicate a spinal tumor).

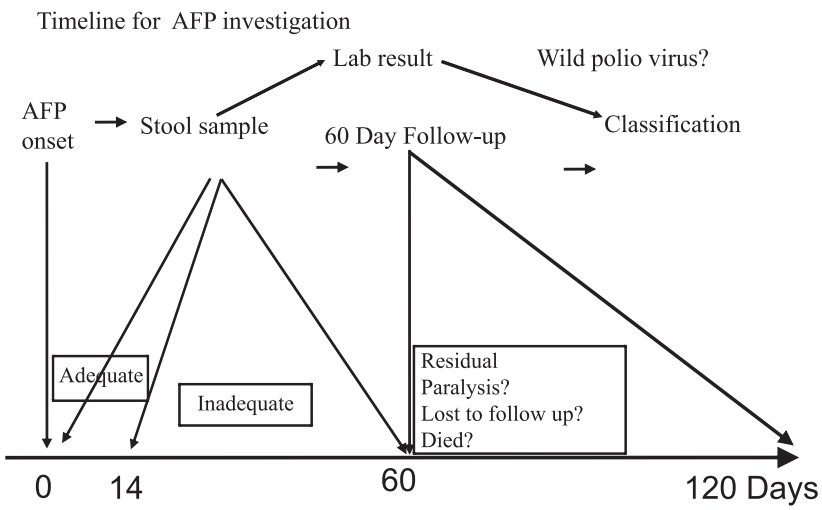

Fig.1. Time line for AFP evaluation

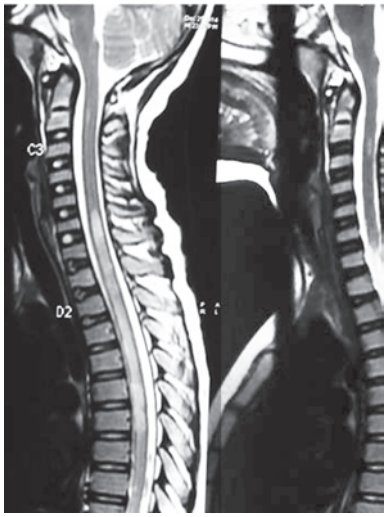

Fig.2.Longitudinally extensive Transverse Myelitis – T2 hyperintensity extending from C5 - T7. Possibilities are NMO Spectrum disorder or Enterovius myelitis

MRI[8]

TM: Up to 40% of cases have no findings on MRI. The Diagnostic sign is T2 hyperintensity which most commonly extends for 3-4 spinal segments with a variable enhancement pattern.

Spinal cord infarct: It is characterized by an enlarged spinal cord, which is hyperintense on T2 weighted images and DWI. The signal intensity abnormality may be limited to the central gray matter. The signal abnormality typically extends over multiple vertebral body segments (Fig.2). The vertebral body T2 hyperintensity may occasionally be seen due to a concomitant infarction.

GBS: Typical findings in GBS are surface thickening and contrast enhancement on the conus medullaris and the nerve roots (anterior nerve roots) of the cauda equina. Contrast is must as non-contrast sequences are essentially normal (Fig.3a,b,c).

MRI in inflammatory myositis may show increased signal intensity in the quadriceps bilaterally (Fig.4)

Management

General principles

All children with AFP need meticulous supportive care. Anticipation and identification of respiratory and bulbar weakness is important. ICU admission will be required if airway obstruction, respiratory failure or significant autonomic disturbance is observed. Management of shock due to reduced vascular tone, management of autonomic instability and complications

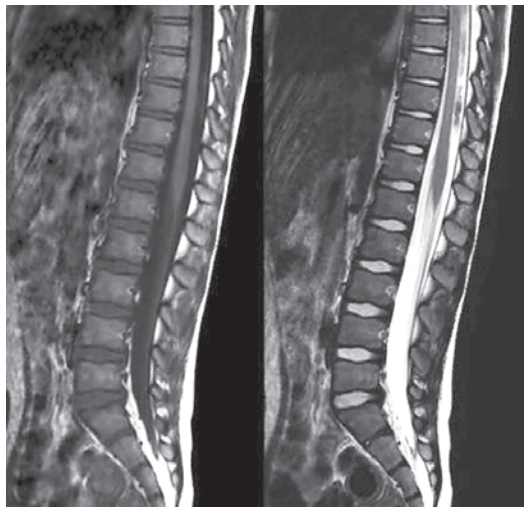

Fig.3a, b.T1 plain and T2 Lumbosacral spine MRI in GBS

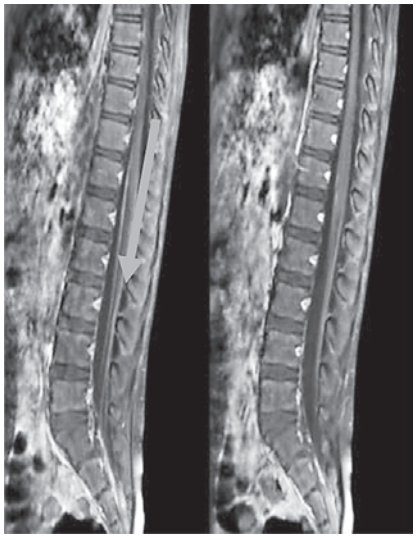

Fig.3C. Radiographic features of GBS contrast T1 MRI lumbosacral. Typical findings in GBS - nerve root thickening and enhancement surrounding the conus and the cauda equina

of immobilization and prevention of nosocomial infections are important considerations. The specific therapy depends on the underlying etiology identified.

TM

Intravenous methyl prednisolone (30 mg/kg up to 1000 mg daily) for five days. Plasma exchange or, intravenous cyclophosphamide (800 to 1200 mg/m^2 administered as a single pulse dose.

GBS

IVIG 400mg/kg/day for 5days in the presence of rapidly progressive weakness (Modified Hughes GBS

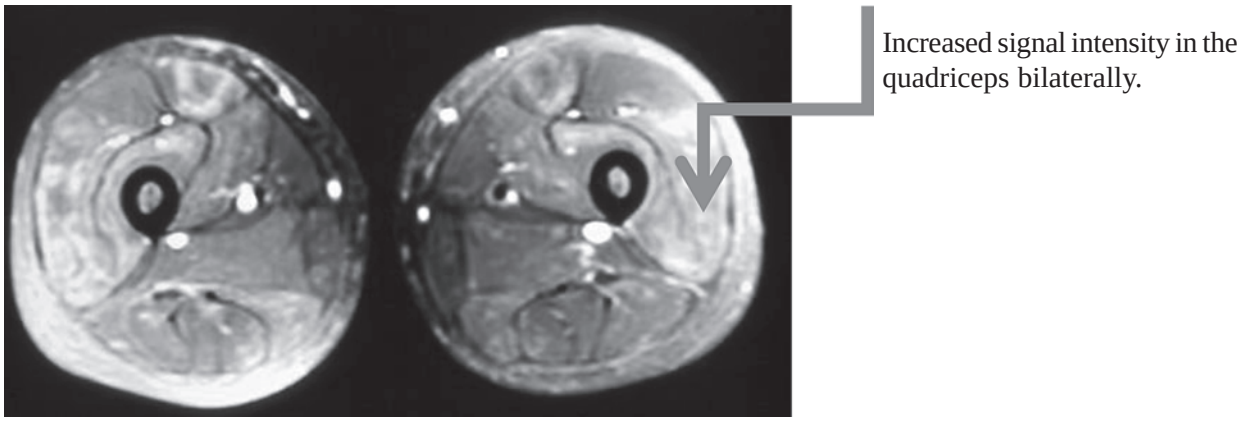

Fig.4. MRI in inflammatory myositis

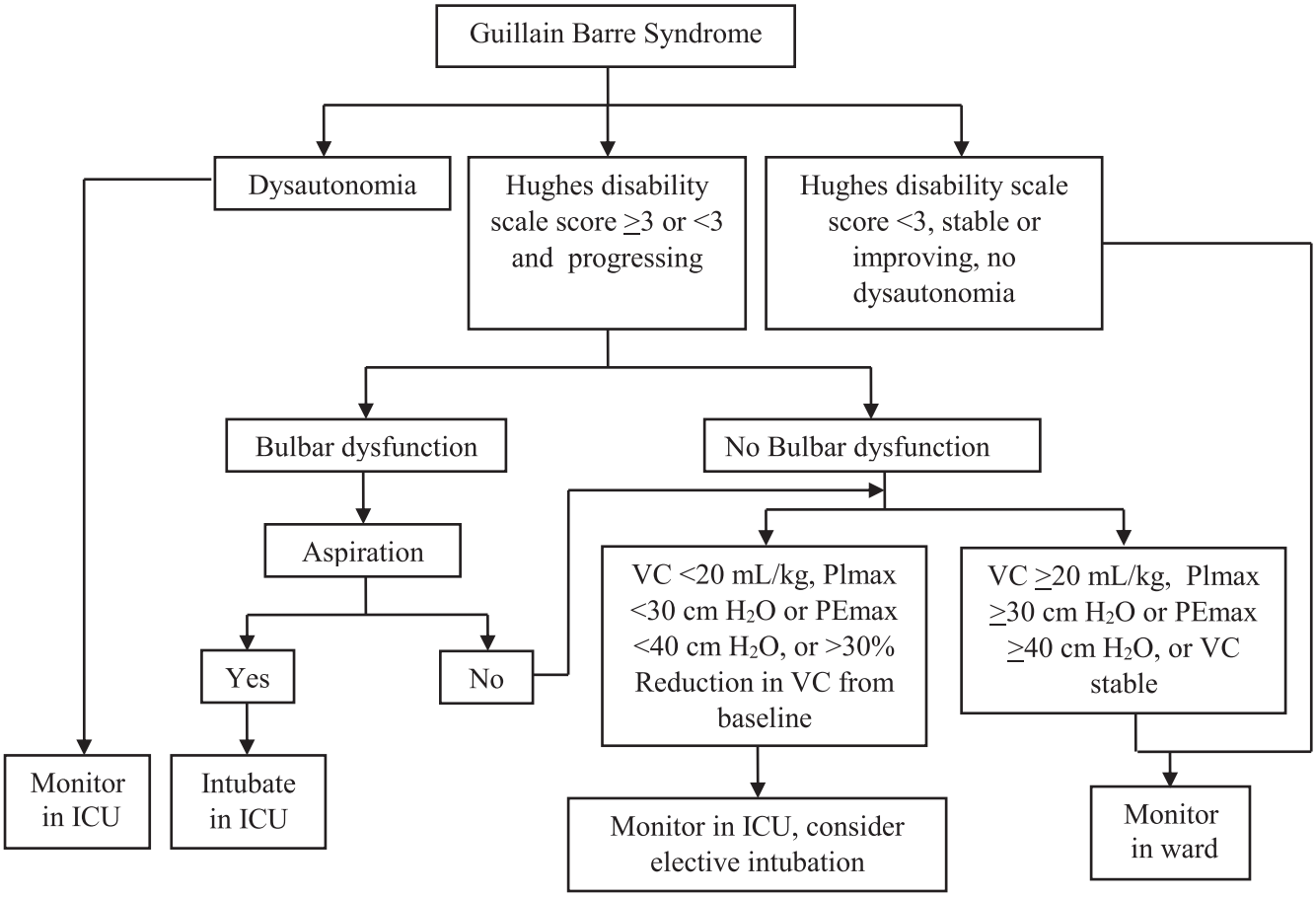

Fig.5. Managment of GBS

PE max- Expiratory pressure; PI max- maximum inspiratory pressure VC vital capacity

AFP surveillance - Current status

disability scale), presence of respiratory or bulbar involvement (Fig.5). Ventilatory support may be required when there is respiratory failure. IVIG is not indicated if the degree of weakness is non-progressive and has been present for more than 4weeks.

AFP surveillance - Current status

There has been a sharp fall in the incidence of poliomyelitis across the world from 350,000 cases in 125 countries in 1988 (year of starting Global Polio Eradication Initiative (GPEI)) to 85 cases in 2 countries

(Pakistan-69 and Afghanistan-16) as of 2019. This was achieved by the active surveillance, immunization and improvement in sanitation. India was declared polio-free on 27 March 2014, three polio free years after the last case was reported in January 2011 in West Bengal. As for world, type 2 virus serotype was declared globally eradicated in 2015 and Type 3 on 24th Oct 2019.

Endgame Polio Strategy 2019-23 is the current strategy by the GPEI. The goals have three major components (Table IV).

India has switched over to bivalent OPV in April 2016 excluding the OPV 2 strain which is mainly responsible for vaccine derived polio. Meanwhile, inactivated polio vaccine (IPV) was introduced in 2016 with two fractional intradermal doses at 6 and 14 weeks along with bivalent OPV.

AFP surveillance is the strategy to screen for circulating wild polio virus in the post-polio eradication phase. The patients with AFP within the last 6 months should be reported to the surveillance Medical Officer of WHO. The four steps of AFP surveillance are finding and reporting children with AFP, transport and analysis of stool sample, identify poliovirus in laboratory and determine the virus strain and origin. Within 48 hours of notification, a trained medical officer investigates the case, proceeds with transportation of stool samples, outbreak response immunizations done in the affected community. A 60 day follow up examination of the case is also done.

The non-polio AFP rate is an indicator of surveillance sensitivity and should be equal to or more than 1: 1,00,000 (background rate of AFP) according to National Polio Surveillance Project.[9]

AFP surveillance is for detecting polio virus transmission.

Outbreak response immunization (ORI)

The incubation period of the polio virus is 4-35 days prior to weakness and all children 0-59 months of age in the affected area (around 500 children) where the child resided or visited in the incubation period are given active immunization. The cases that are likely to be polio in the community are also actively investigated by the SIO and in AFP cases with inadequate stool specimen, 60 day follow up is done between 60 and 90 days.

The post certification strategy is also developed to maintain a polio free world. Its goals are

1. Contain poliovirus sources by ensuring that they are controlled and removed
2. Withdraw OPV and immunize with IPV against possible re-emergence of any polio virus
3. Defect and respond promptly to any polio virus reintroduction.

The trivalent OPV which was in use till 2016 had a highest sero conversion rates for type 2 and hence wild polio virus type 2 was eradicated in 1999. Most cases of vaccine derived Polio Myelitis are due to OPV 2 and the trivalent OPV was withdrawn and replaced with bivalent OPV since April 2016.

Conclusion

AFP is a complex clinical syndrome that requires immediate and careful evaluation of the differential diagnoses. Each case of AFP is an emergency from both clinical and public health perspective. The precise knowledge of the etiology, underlying pathophysiologic mechanisms and anatomic changes have profound implications for prognosis and treatment. The role of

Table IV. Endgame Polio Strategy 2019-23 – Goals

Goal one: *Eradication*	Interrupt transmission of all wild poliovirus (WPV) Stop all circulating vaccine-derived poliovirus (cVDPV) outbreaks within 120 days of detection and eliminate the risk of emergence of future VDPVs
Goal two: *Integration*	Contribute to strengthening immunization and health systems to help achieve and sustain polio eradication Ensure sensitive poliovirus surveillance through integration with comprehensive vaccine preventable disease (VPD) and communicable disease surveillance systems Prepare for and respond to future outbreaks and emergencies
Goal three: *Certification & containment*	Certify eradication of WPV Contain all polioviruses

infectious agents and immune processes as significant causes of AFP are complemented by different natural and man made toxins. Epidemiologic and clinical surveillance require detailed knowledge of the potential differential diagnosis of AFP. Clinicians must be aware of the causes of AFP and of the need to continuously investigate AFP cases. The health workers also need to be aware of the need for reporting all AFP cases, collecting stool specimens and testing for the poliovirus.

Points to Remember

- ***Clinical features of polio must be taught to the younger residents as imported or vaccine associated polio can still occur***
- ***GBS requires prompt diagnosis and management and it is the major AFP now because of the spurt of various viral infections.***
- ***Transverse myelitis (TM) and traumatic neuritis are the other common causes of AFP.***
- ***TM with long segment involvement may be mistaken for GBS because of lack of sensory level and prolonged spinal shock which may be due to enterovirus related TM, or NMO (neuromyelitis optica).***
- ***In TM preservation of dorsal column (joint position sensation) → Anterior cord syndrome → Anterior spinal artery occlusion***
- ***Rabies can present with features of GBS.***

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CLIPPINGS

High-flow nasal cannula therapy as apneic oxygenation during endotracheal intubation in critically ill patients in the intensive care unit: a systematic review and meta-analysis.

Hypoxemia, a frequently reported complication of intubation, is considered a predisposing factor for cardiac arrest and death. Therefore, oxygenation during endotracheal intubation plays an important role in prolonging the maintenance of acceptable oxygen saturation levels. Authors conducted asystematic review and meta-analysis to assess the clinical efficacy of high-flow nasal cannula (HFNC) therapy as apneic oxygenation in critically ill patients who require endotracheal intubation in the intensive care unit (ICU).Review included six randomized controlled trials and a prospective study identified in PubMed, Embase, Cochrane Library, and the Web of Science until August 18, 2019 involving 956 participants Risk ratio of severe hypoxemia decreased with increasing baseline partial oxygen pressure (PaO_2) to fraction of inspired oxygen (FiO_2) ratio in the study group. In subgroup analysis, HFNC significantly reduced the incidence of severe hypoxemia during endotracheal intubation in patients with mild hypoxemia (PaO_2/FiO_2> 200mmHg. The authors concluded that HFNC was non inferior to standard of care for oxygen delivery during endotracheal intubation and was associated with a significantly shorter ICU stay. The beneficial effect of HFNC in reducing the incidence of severe hypoxemia was observed in patients with mild hypoxemia.

NEUROLOGY

NEWER INTERVENTIONS IN EPILEPSY MANAGEMENT

Ramalakshmi Ramiah

Abstract: *Epilepsy is a global issue affecting about 70 million people among the world population. Nearly 80% of them live in low and middle-income countries with limited resources. Although highly advanced treatment is available in some countries, up to 90% of people with epilepsy are not adequately treated or are not treated with conventional antiepileptic therapy in resource limited countries.*

This review will highlight a few of the newer advances in management of epilepsy in children. They include pharmacological interventions, ketogenic diet, early genetic diagnosis and newer model multi-disciplinary team management of children with epilepsy.

Keywords: *Epilepsy, Treatment, Advances.*

Epilepsy is a global issue affecting about 70 million people worldwide. Nearly 80% of them live in low and middle-income countries with limited resources. An estimated 2.4 million people are diagnosed with epilepsy each year.[1] Although highly advanced treatment is available in some countries and parts of Asia, most of the people with epilepsy are not managed appropriately in developing countries.

Epilepsy in children differs from epilepsy in adults both in seizure type and epilepsy syndrome. The decision to treat is based on a careful evaluation of the balance between the likelihood of further seizures and the risk of adverse effect of the treatment. The aim of the treatment is to abolish seizures completely and at the same time keeping the side effects of the treatment to a minimum. It is generally reported that between 20-40% will have refractory epilepsy.[2] Refractory epilepsy increases the risk of cognitive deterioration, psychosocial dysfunction and sudden unexpected death. The treatment goal should be focused on preservation of social, vocational and cognitive performance and minimising complications.

This review will highlight newer advances in the management of epilepsy in children. They include pharmacological interventions (Perampanel, cannabinoids), ketogenic diet (KD), early genetic diagnosis and newer model multidisciplinary. Team management of patients with epilepsy. Epilepsy surgery has an important role in the management of refractory epilepsy but is beyond the scope of this article.

Good practice principles in medical management of epilepsy

Medical management of epilepsy is complex and has to be tailored to the individual patient. The management is variable in different parts of the world based on local availability of resources. Drug therapy remains the mainstay of management of epilepsy in children. Monotherapy is generally preferred to minimize the risk of adverse effects. If the treatment fails, it is preferable to try alternative monotherapy before moving on to combination treatment. Children who continue to have seizures on monotherapy are sometimes prescribed a long term second drug in addition.

Combining anti-epileptic drugs (AEDs) requires an understanding of their pharmacology, particularly their mechanisms of action. Other issues that must be considered in planning a treatment regimen for the individual patient include spectrum of efficacy, side-effect profile and propensity for adverse interactions. In the United Kingdom, National Institute of Health and Care Excellence (NICE) has formulated guidance for medical management of epilepsy.[3] Tables I and II summarize the guidelines for clinicians to choose an appropriate anti-epileptic medication based on the epilepsy syndrome and type of seizures.

Newer pharmacological interventions

Perampanel: Perampanel is a highly selective, non-competitive AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist. The mechanism of action is that it reduces neuronal

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Table I. NICE guidelines on AEDs based on seizure types

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (that may worsen seizures)
Generalised tonic–clonic	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate Topiramate	Clobazam Lamotrigine Levetiracetam Sodium valproate		(If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy suspected) Carbamazepine Gabapentin Oxcarbazepine Phenytoin, Pregabalin, Tiagabine, Vigabatrin
Tonic or atonic	Sodium valproate	Lamotrigine	Rufinamide Topiramate	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine, Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Clobazam, Clonazepam, Levetiracetam Topiramate Zonisamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin, Pregabalin Tiagabine, Vigabatrin
Myoclonic	Levetiracetam Sodium valproate Topiramate	Levetiracetam Sodium valproate Topiramate	Clobazam, Clonazepam, Piracetam Zonisamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin, Pregabalin Tiagabine, Vigabatrin
Focal	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate Lacosamide, Phenobarbital Phenytoin, Pregabali Tiagabine, Vigabatrin, Zonisamide	
Prolonged or repeated seizures and convulsive status epilepticus in the community	Buccalmidazolam Rectaldiazepam Intravenous lorazepam			
Convulsive status epilepticus in hospital **Refractory convulsive status epilepticus**	Intravenous lorazepam diazepam Buccal midazolam Intravenous midazolam Propofol (not in children) Thiopentalsodium	Intravenous phenobarbital Phenytoin		

Table II. NICE guidelines on AEDs based on epilepsy syndromes

Epilepsy syndrome	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiarycare	Do not offer AEDs (may worsen seizures)
Childhood absence epilepsy or other absence syndromes	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Clobazam, Clonazepam Levetiracetam Topiramate Zonisamide Vigabatrin	Carbamazepine Gabapentin Oxcarbazepine, Phenytoin Pregabalin, Tiagabine
Juvenile absence epilepsy or other absence syndromes	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Clobazam, Clonazepam Levetiracetam Topiramate, Zonisamide	Carbamazepine Gabapentin Oxcarbazepine, Phenytoin Pregabalin, Tiagabine Vigabatrin
Juvenile myoclonic epilepsy	Lamotrigine Levetiracetam Sodium valproate Topiramate	Lamotrigine Levetiracetam Sodium valproate Topiramate	Clobazam, Clonazepam Zonisamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin, Pregabalin Tiagabine Vigabatrin
Epilepsy with generalised tonic -clonic seizures only	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Clobazam Lamotrigine Levetiracetam Sodium valproate Topiramate		
Idiopathic generalised epilepsy	Lamotrigine Sodium valproate Topiramate	Lamotrigine Levetiracetam Sodium valproate Topiramate	Clobazam, Clonazepam Zonisamide	Carbamazepine Gabapentin Oxcarbazepine, Phenytoin Pregabalin, Tiagabine Vigabatrin
Infantile spasms not due to tuberous sclerosis	Discuss with, or refer to, a tertiary paediatric epilepsy specialist Steroid (prednisolone or tetracosactide) or vigabatrin			
Infantile spasms due to tuberous sclerosis	Discuss with, or refer to, a tertiary paediatric epilepsy specialist Vigabatrin or steroid (prednisolone or tetracosactide)			

Epilepsy syndrome	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Benign epilepsy with centrotemporal spikes	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate Lacosamide Phenobarbital, Phenytoin Pregabalin, Tiagabine Vigabatrin, Zonisamide	
Panayiotopoulos syndrome	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate, Lacosamide Phenobarbital, Phenytoin, Pregabalin, Tiagabine, Vigabatrin, Zonisamide	
Late-onset childhood occipital epilepsy (Gastaut type)	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepin acetate Lacosamide Phenobarbital, Phenytoin, Pregabalin, Tiagabine, Vigabatrin, Zonisamide	
Dravet syndrome	Discuss with, or refer to a tertiary paediatric epilepsy specialist Sodium valproate Topiramate	Clobazam Stiripentol		Carbamazepine Gabapentin, Lamotrigine Oxcarbazepine Phenytoin, Pregabalin Tiagabine, Vigabatrin
Continuous spike and wave during slow sleep	Refer to a tertiary paediatric epilepsy specialist			
Lennox-Gastaut syndrome	Discuss with, or refer to a tertiary paediatric epilepsy specialist Sodium valproate	Lamotrigine	Felbamate Rufinamide Topiramate	Carbamazepine Gabapentin Oxcarbazepine Pregabalin, Tiagabine Vigabatrin
Landau-Kleffner syndrome	Refer to a tertiary pediatric epilepsy specialist			
Myoclonic astatic epilepsy	Refer to a tertiary pediatric epilepsy specialist			

hyperexcitability by targeting glutamate activity at postsynaptic AMPA receptors. It is approved as an adjunct therapy for focal-onset seizures and primary generalized tonic-clonic seizures (GTCS) in patients aged 12 years and older.[4] A multicentre, randomized, double-blind, placebo-controlled study, has demonstrated a 23.3% to 27.2% reduction in focal-onset seizures when perampanel is used as adjunctive treatment.[5] In a placebo controlled study in 164 patients aged 12 years and older with GTCS, a reduction in seizure frequency was observed in the perampanel group. 30.9% of patients treated with perampanel were free of Primary generalized tonic-clonic seizures, compared to 12.3% in the placebo group during the 13-week maintenance period.[4]

Perampanel is once-daily dosing and has a half-life of 106 hours. Enzyme-inducing antiepileptic drugs can reduce perampanel plasma concentrations and decrease its efficacy.[5]Themost common adverse events are dizziness, fatigue, headache and somnolence. Specific adverse effects to monitor are neuropsychiatric events, including aggression, anger, homicidal ideation, hostility, and irritability. These side effects are dose-related and most often occur in the first 6 weeks of therapy. The combination of alcohol and perampanel significantly worsened mood and increased anger and the product labelling recommends avoiding the use of alcohol while on therapy with perampanel.[6]

Cannabidiol (CBD): Cannabinoids have been recognized to have a role in treatment of resistant epilepsy. The history of cannabis being used in treatment of various medical conditions dates back to perhaps as early as 4000 BC. In 1843 O'Shaughnessy W.B reported successful treatment of a 40days old infant with seizures. In 1937 following the marijuana act, scientific community lost interest in exploring cannabis as an anti-epileptic drug. In the 1970s and 80s there were reports of reduction in seizure frequency after smoking cannabis. Mechoulam and Carlini, in 1978 conducted the first human epilepsy trial.

Widespread community interest in cannabinoid products for epilepsy has grown as a consequence of social media reports of successful treatment in individual children. While the precise mechanisms by which CBD exerts its anticonvulsant properties in humans remain unknown, growing evidence suggests CBD reduces neuronal hyperexcitability through a unique multimodal mechanism of action. Itantagonizes G protein-coupled receptor 55 (GPR55) at excitatory synapses. The inhibition of intracellular calcium release decreases excitatory currents and seizure activity. CBD desensitizes transient receptor potential vanilloid type 1 (TRPV1) channels. The resultant decrease in extracellular calcium influx decreases neurotransmission. CBD inhibits equilibrative nucleoside transporters (ENT1), reducing adenosine reuptake. The increase in extracellular adenosine reduces hyper excitability and neurotransmission.[7] CBD is metabolized in the liver by CYP2C19 and CYP3A4 enzymes and UDP glucuronosyltransferase 1 family, UGT1A7 and UGT2B7 isoforms. Peak plasma concentration (Tmax) is 2.5 to 5 hours. It is excreted in stools with minor renal clearance. Co-administration of CBD with clobazam, produce a 3-fold increase in plasma concentration of N-desmethylclobazam. Concomitant use of CBD and valproate increases the incidence of elevation of liver enzymes.

Open label study of Devinsky, et al (2016) included children and adolescents with refractory epilepsy.[8] Overall 36.5% reduction in seizures was reported. There was significant variability in daily dosage (up to 25 mg/kg/day). This study reported adverse events including somnolence, diarrhea and fatigue. Rosenberg (2016) performed a post study analysis of Quality of Life in Childhood Epilepsy (QOLCE) surveys in 20 patients.[9] Significant improvements in global scores and several sub scores were reported.

Thiele, et al (2018) enrolled 171 patients with Lennox-Gastaut syndrome (LGS) who were randomized to receive CBD or placebo.[10] A 2 weeks dose escalation of CBD to 20 mg/kg/day over two weeks and 12 weeks maintenance was used in this study. There was a monthly reduction in atonic seizures frequency by 43.9% in CBD group compared to 21.8% in placebo group (p=0.0096).There was also a monthly reduction in all seizure types by 41/2% in CBD group compared to 13.7% in placebo group (p=0.0004).

NICE guidelines published in December 2019 states that cannabidiol with clobazam is recommended as an option for treating seizures associated with Dravet syndrome and LGS in patients aged 2 years and older, only if the frequency of convulsive seizures is checked every 6 months. Cannabidiol is stopped if the frequency has not fallen by at least 30% compared with 6 months before starting treatment.[11,12,13]

Non-pharmacological intervention

Ketogenic diet (KD)**:** It is a high fat, low carbohydrate and adequate protein diet well-established as treatment option for drug resistant childhood epilepsies. KD was first described in the medical literature in 1921 as a treatment for epilepsy in children, following other reports of the beneficial effects of fasting on seizure control. The diet

was designed to mimic the metabolic changes that occur in the body during starvation, i.e. adaption to spare muscle protein breakdown and draw on energy reserves of body fat. Muscles and other tissues progressively switch energy source from glucose to free fatty acids which are converted to ketone bodies (acetoacetate and beta-hydroxybutyrate); these become the primary energy substrate for brain and other metabolically active tissues in the absence of adequate glucose supply. This state of ketosis is characterized by the rising levels of ketone bodies which can be measured in the blood or urine. This diet was known as the 'ketogenic diet' and is the basis of the classical ketogenic diet still used today.

This classical diet is based on a ratio of ketone producing foods in the diet (fat) to foods that reduce ketone production (carbohydrate and protein). A 'ketogenic' ratio of at least 3:1 is usually needed for maintenance of a good state of ketosis and optimal seizure control, although this varies between individuals and some will need a lower (2:1) or a higher (4:1) ratio. In a 3:1 diet, 87% of the energy is provided by fat, in a 4:1 diet this increases to 90%. Protein intake is based on minimum requirements for growth and is generally provided by a high-biological value source at each meal. Carbohydrate is very much restricted; the main sources being a limited portion of vegetables or fruit.

The medium chain triglyceride (MCT) ketogenic diet was developed in the 1970s as an alternative to the classical diet. MCT is absorbed and transported more efficiently in the body than other types of fat and will yield more ketones per unit of dietary energy. Therefore less total fat is needed on the MCT diet allowing more protein and carbohydrate food sources to be included. The traditional MCT diet which provided a higher amount of energy from MCT however led to reports of gastro-intestinal problems in some children and a modified version with less MCT was suggested.

The first RCT of the KD to demonstrate effectiveness in children aged 2-16 years was published in 2008.[14] In this trial, 145 children aged 2-16 years, who had failed at least two AEDs and had at least seven seizures weekly, were randomized to receive a KD, either immediately or after a 3-month delay with no additional treatment changes (the latter being the control group). After 3 months, the mean percentage of baseline seizures (on an intention-to-treat analysis) was significantly lower in the diet group (62%) than in controls (13.7%, $p<0.0001$). Twenty-eight (38%) of the diet group had greater than 50% seizure reduction, compared to four (6%) in control group ($p<0.0001$). A randomized controlled trial of both classical and MCT ketogenic diets did not find either type of diet to be significantly better in terms of efficacy or tolerability, concluding both diets have their place in the treatment of childhood epilepsy. The efficacy of the classical ketogenic diet for children with refractory epilepsy has been strongly supported by 2 randomized controlledtrials.[14, 15] For children with glucose transporter type 1(GLUT1) deficiency or pyruvate dehydrogenase complex deficiency, ketogenic diet is the treatment of first choice.[16]

Constipation was the most commonly reported adverse event of the ketogenic diet. One of the long-term concerns of the classical ketogenic diet is its negative effect on physical growth due to its limited protein content.[17] The ketogenic diet variant with medium chain triglycerides has the advantage of allowing a higher amount of protein and carbohydrates compared to the classical ketogenic diet. Still, no significant differences in growth were found between the classical and medium-chain triglycerides diet groups after 12 months, despite the significantly higher protein intake in the medium-chain triglyceridesdiet.[17]

In the past, neonates and infants were infrequently treated with the KD. However in a study by Dressler, et al the advantages of early use of the KD before 1.5 years of age and after 1.5 years of age was studied.[18] There were no significant differences between groups with respect to responder rates (63.8% vs 57.9 at 3 months), but more infants became seizure free (34.5% vs 19% at 3 months; 32.7% vs 17.5% at 6 and 12 months respectively. A significantly higher number of infants remained seizure free in the long term ($p= 0.001$). The study concluded that in infants with infantile spasms, LGS, myoclonic astatic epilepsy (MAE) and focal epilepsy, efficacy of KD has been shown high. The study recommended early use of KD in infancy as seizure freedom is essential for good developmental outcome.

Diagnostic intervention: Genetic testing

Targeted genetic testing plays an integral part of management of early onset infantile and refractory epilepsies in children. Identification of the causative mutation affects treatment as well as prognostic and genetic counselling. A number of studies have found a risk of 2%-4.6% for individuals with an affected first-degree relative.[19] Although this represents a doubling of risk, over 75% of individuals with a positive family history have only one affected relative and few families follow Mendelian patterns ofinheritance.[20]

Many types of epilepsy have a genetic component; this includes those that are largely genetic such as the genetic generalized epilepsies (GGE, previously called the

idiopathic generalized epilepsies). In contrast to the common self-limited generalized and focal epilepsies, there are many severe monogenic epilepsy syndromes where molecular testing has a key role in clinical practice today. Important examples include SCN1A (voltage-gated neuronal sodium channel) mutations associated with Dravet syndrome.

Advances in genomic technologies such as microarray-based comparative genomic hybridization (CGH) and DNA sequencing have revealed hundreds of heterogeneous pathogenic variants in patients with neuro developmental disorders, including epilepsy. In recent years, the importance of copy number variation (CNV), where variable numbers of genes exist, such as deleted or duplicated genes, has come to be recognized as part of normal human variation. CNVs are more likely to be pathogenic if they are larger. CNV testing by single nucleotide polymorphism (SNP) microarray or array comparative genomic hybridization (CGH) is also known as molecular karyotyping.

Early infantile epileptic encephalopathy (EIEE) is a devastating epilepsy syndrome with onset in the first months of life. Different countries are offering gene panel testing of varying numbersof genes tested and whole exome sequencing.

In a study by Ostrander, et al they applied whole-genome analysis (WGA) consisting of whole-genome sequencing and comprehensive variant discovery approaches to a cohort of 14 EIEE subjects for whom prior genetic tests had not yielded a diagnosis.[18] The study identified both de novo point and INDEL mutations and de novo structural rearrangements in known EIEE genes, as well as mutations in genes not previously associated with EIEE. The detection of a pathogenic or likely pathogenic mutation in all 14 subjects demonstrated the utility of WGA to reduce the time and costs of clinical diagnosis of EIEE. While exome sequencing may have detected 12 of the 14 causal mutations, 3 of the 12 patients received non-diagnostic exome panel tests prior to genome sequencing. Thus, given the continued decline of sequencing costs, their results supported the use of WGA as an efficient strategy for the clinical diagnosis of EIEE and other genetic conditions.[21]

Multidisciplinary care model

Nurse practitioners (NP) / Epilepsy Nurse Specialist(ENS): Epilepsy centers are increasingly employing multidisciplinary teams as a means to extend the availability of neurologic outpatient services.[22] Nurse practitioners (NPs) offer a particular skillset of clinical expertise and counseling that is pertinent to epilepsy care, however, the result of their addition has not yet been well-characterized. Although epilepsy nurse specialists are used in the United Kingdom, a systematic review did not find strong evidence of benefit in clinical outcomes or patient satisfaction.[23] A 2016 Cochrane review concluded that epilepsy specialist NPs may improve the knowledge, compliance and quality of life of patients with epilepsy.[24] A study comparing physician only care model and NP/ENS - physician care team, found that both care models exceeded 90% adherence for the objective quality measures of documentation of seizure frequency, offering an intervention to reduce seizures and documenting or ordering testing for seizure etiology. With a longer follow-up period, the improved safety counseling provided by the NP-physician team care model may decrease mortality and morbidity. Furthermore, greater recognition of behavioral and psychiatric comorbidities may improve quality of life. There is evidence that epilepsy specialist nurses provide less costly consultation than physicians and that epilepsy specialist NPs can considerably reduce the primarycare costs associated with patients with epilepsy.[23, 24] This study suggests that employment of a NP–physician team can increase availability of care without compromising quality of care.

Surgery in resistant epilepsy

Epilepsy surgery is an effective way to control seizures in patients with drug-resistant epilepsy, often leading to improvements in cognition, behaviour, and quality of life. The effectiveness of surgical treatment depends on epilepsy type, underlying pathology, and accurate localisation of the epileptogenic brain region by various clinical, neuroimaging, and neurophysiological investigations. The surgical options include resective surgery and palliative surgery. Few of the resective surgical procedures include temporal lobe resections, extra temporal lobe resections and hemispherectomy. Palliative epilepsy surgical procedures include corpus callasotomy and Multiple Subpial Transections (MST). Minimally invasive procedures include neurostimulation procedures including Deep brain stimulation, Vagal Nerve stimulation and Responsive neurostimulation. Vagus nerve stimulation is applicable for drug-resistant epilepsy patients where resection of the lesion is not possible and for drug-resistant epilepsy patients with a previous history of surgical treatment failure. Responsive neurostimulation is a new technology that can discover epilepsy seizure activities in the brain through monitoring electrocorticographic activity, and to give a direct focal electrical stimulation, so as to

reduce epilepsy seizure through the targeted way.[25] Other minimally invasive surgical interventions include Stereotactic Radiosurgery and Stereotactic Laser Ablation (SLA). In stereotactic Radiosurgery, by focusing on the ionizing radiation targeted to the deep lesions, this method can avoid the damage to the surrounding tissue. When the epileptogenic zone is located in the deep brain or the important structure of the brain, which is not suitable to do the surgery, the stereotactic laser ablation may be a good choice.[25]

Conclusion

Though pharmacotherapy is the main modality of treatment in most epilepsies, ketogenic diet should be considered early in specific epileptic syndromes. Recent technological advances have resulted in newer drugs which have helped to reduce the seizure burden in patients with refractory epilepsy and to improve quality of life. Genetic testing aids early diagnosis, targeted treatment and avoidance of abundance of investigations. Continuing research will be needed for further advances in targeted treatment of genetic epilepsies.

Points to Remember

- ***Epilepsy in children can differ from epilepsy in adults both in seizure type and epilepsy syndrome.***
- ***Medical management of epilepsy is complex and has to be tailored to the individual patient. Monotherapy is generally preferred.***
- ***If the monotherapy fails, it is considered preferable to try alternative monotherapy.***
- ***Children who continue to have seizures on monotherapy are prescribed a long term second drug in addition.***
- ***Pharmacotherapy with newer drugs and nonpharmacological therapy like ketogenic diet useful in certain resistant epilepsy.***
- ***Genetic testing aids in diagnosis.***

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CLIPPINGS

Sinclair JC, Haughton DE, Bracken MB, Horbar JD, Soll RF. Cochrane neonatal systematic reviews: a survey of the evidence for neonatal therapies. Clin Perinatol 2003; 30(2):285-304.

A survey is reported of 113 systematic reviews of therapies in neonatology, based on 559 eligible randomized trials in total. These reviews were prepared by the CNRG and were published in the Cochrane Library, Issue 3,2001. The median number of included trials per review was 3 (range 0 to 32) and participants 207 (range 0 to 5460). Among 90 reviews with a categorical primary outcome, the median number of outcome events per review was 54 (range 1 to 1284). Among reviews finding a statistically significant benefit of treatment, the effect size was large (median relative risk 0.55, range 0.09 to 0.93). Reviews of surfactant for prevention and treatment of respiratory distress syndrome were able to detect moderate-sized treatment effects (median relative risk 0.85) because of the large number and size of trials in this field. Among many reviews finding no evidence of treatment effect, large and potentially important benefits or harms could not be excluded. Most CNRG reviews were current. There is a continuing need to prepare systematic review of therapies not yet covered and to keep an increasing number of reviews up-to-date.

Study of lung ultrasonography as a diagnostic tool in childhood pneumonia.

According to current guidelines, pneumonia is diagnosed by clinical history, respiratory rate, fever, respiratory signs, and symptoms. A cross-sectional study was undertaken to compare chest ultrasonogram with chest radiography (CXR) in the diagnosis of 60 children. with fever and signs of respiratory distress, and they were divided in two groups: group I with pneumonia, which included 45 patients who were finally diagnosed as having clinically evident pneumonia, and group II without pneumonia.

Lung ultrasonography could detect consolidation in more than one lobe than CXR (P = 0.048). Authors have conlcluded that chest ultrasonogram offers an important contribution to the diagnostic procedures of pleuropulmonary disorders in children, such as pneumonia and pleural effusion, with higher sensitivity, specificity, and positive predictive index compared with CXR.

Elmashad GM, Bahbah WA, Mousa WA, Shalaby MM. Study of lung ultrasonography as a diagnostic tool in childhood pneumonia. Menoufia Med J 2019; 32:1043-50.

NEUROLOGY

NEUROIMAGING

Leema Pauline

Abstract: *Availability of neuroimaging facilities has made the evaluation of neurological problems easier in the last few decades. Computed tomography scan of brain is the initial choice in very sick children because of its wider availability, faster turnaround time and lower cost. Cranial ultrasonography is an important modality in the follow up of infants in the postnatal period, particulary in the evaluation of hypoxic ischemic encephalopathy, subependymal- periventricular- intraventricular hemorrhage and hydrocephalus. It is used as a point of care investigation by neonatologists. Absence of radiation exposure and precision makes magnetic resonance imaging the modality of choice in emergency situations. But the disadvantages are the need for sedation or brief anaesthesia, longer procedural time and cost. But benefits outweigh the disadvantages and additional tools like Magnetic resonance angiography, Magnetic resonance venography and Magnetic resonance spectroscopy add precious information for further evaluation.*

Keywords: *Neuroimaging, Cranial ultrasonography, CT, MRI, MRV, MRA, MRS.*

Neuroimaging plays an important and growing role in the diagnosis and management of neurological diseases in children. Neuroimaging falls into two broad categories (a) structural imaging deals with the structure of the brain and (b) functional imaging is used to measure the brain function; it is useful for diagnosing metabolic diseases and as a research tool in cognitive neurosciences including neuropsychology.

Modalities of neuro imaging

The major imaging modalities for structural and functional evaluation of the central nervous system (CNS) are ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine techniques. USG and CT provide rapid screening for gross macro structural abnormalities. MRI often provides the most definitive macro structural, micro structural and functional imaging information. Nuclear medicine techniques may offer additional functional data.

X-ray skull

Plain films of the skull can show fractures of the skull, erosions, hyperostosis, calcifications, overriding of sutures (craniostenosis), widening of sutures (raised intra cranial pressure) and inflammation of the sinuses and mastoids. Skull X-rays are rarely used nowadays because of their low yield and have been replaced by computed tomography.

Ultrasonogram cranium

Cranial ultrasonography is the most frequently used neuroimaging modality in prenatal and perinatal period. Developmental anomalies of central nervous system such as holoprosencephaly, lissencephaly, encephalocele, Dandy walker malformation, spina bifida, hydrocephalus etc., can be detected by sonography. In newborns, open anterior fontanel provides an excellent window to visualize the infant brain. It is helpful in the evaluation of hypoxic ischemic encephalopathy, subependymal- periventricular-intraventricular hemorrhage, hydrocephalus and major migrational anomalies such as agyria- pachygyria complex.

Computed tomography

Computed tomography has been available since 1970s for clinical use and is widely available for emergencies and medically unstable patients. Lesions appearing as low density (appearing dark) include edema, infarct, inflammation, necrosis and cysts. High density (appearing bright) lesions include calcifications and hemorrhage. Fat containing lesions appear less dense and air appears as the lowest density. Modern CT devices allow appropriate visualization of midline structures and the ventricular system, providing sufficient diagnostic yield for herniation and hydrocephalus. However, CT is generally suboptimal for imaging of structures in the posterior fossa and brain stem. The greatest practical advantage of CT, particularly over MRI, is its greater availability, much faster imaging time, lower cost and in the context of known or suspected metallic foreign bodies, when MRI is contraindicated.[1]

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Magnetic resonance imaging

Magnetic resonance imaging is the most powerful neuro imaging modality for adults and children. Painless and noninvasive, MRI uses powerful magnets and radio waves to produce excellent detailed images of the brain. It provides multiplanar imaging with high resolution without repositioning the patient. However it has less tolerance for patient movement and hence sedation is required for most of the children.[2]

Cerebrospinal fluid, muscle, deoxyhemoglobin, hemosiderin and substances with long T1 relaxation times appear dark on T1W (T1 weighted) images. Tissues with short T1 relaxation time such as fat, methemoglobin appear bright on T1W images. On T2W images, structures with long T2 relaxation times such as CSF, edema, infarct, tumours, demyelination appear bright whereas muscle, deoxyhemoglobin, and hemosiderin appear dark because of short T2 relaxation times.

Patients with paramagnetic metallic implants such as aneurysm clips, brain stimulators (deep brain stimulator or vagus nerve stimulator) or pacemakers are ineligible for MRI. These metallic foreign bodies could move or heat up, resulting in injuries to surrounding tissues. In a closed type MRI system, patients with claustrophobia may be unable to remain still during the procedure. Similarly, children or patients with cognitive or behavioral impairments may not be able to undergo the test. This obstacle can sometimes be overcome with the use of sedation or with use of newer open MRIs.[3]

The various neuroimaging findings in different neurological conditions are discussed below:

Neuro infections

Viral infections: Viral infections of central nervous system can take the form of meningitis, encephalitis, encephalomyelitis or encephalomyeloradiculitis. Neurotropic viruses have special predilection for certain regions of the neuraxis producing characteristic imaging features that may aid in prioritizing diagnostic considerations in the differential diagnosis (Table I).[4,5]

Bacterial meningitis: Neuroimaging is neither sensitive nor specific for the diagnosis of meningitis. Abnormal enhancement of the pia and arachnoid (leptomeninges) caused by inflammatory breakdown of the blood-brain barrier is seen in only 50% of patients.[6] Neuroimaging is most useful for excluding herniation before lumbar puncture and for detecting complications such as subdural effusion / empyema (Fig.5), ventriculitis (Fig.6&7), hydrocephalus (Fig.8), sinus venous thrombosis, infarct and cerebral abscess. Similar to parenchymal abscess, pus in the ventricles or epidural or subdural space shows restricted diffusion, a finding that is useful for distinguishing simple effusion from empyema in the context of acute bacterial meningitis.[7]

Table I. Characteristic imaging features in certain viral infections

Viral infection	Characteristic imaging features
Herpes simplex virus (Fig.1)	Inferomedial temporal lobe, insula, limbic system
Japanese encephalitis virus (Fig.2)	Thalamus (90%), basal ganglia, substantia nigra
West Nile virus	Thalamus, basal ganglia, cranial nerves, spinal cord, cauda equina
Dengue virus	Globus pallidi, thalami, hippocampus, temporal lobe, pons, spinal cord
Chikungunya virus	Cerebral white matter, cauda equina
Rabies virus	Brainstem, hippocampus, limbic system, hypothalamus
Human immunodeficiency virus	Symmetric periventricular white matter involvement, cerebral atrophy
Entero virus (Fig.3)	Medulla, pons, midbrain, splenium of corpus callosum
Epstein-Barr virus	Cerebellum, pons, cerebral peduncles, splenium of corpus callosum
Measles virus	Bilateral striatal necrosis, ADEM pattern
Varicella encephalitis	Cortex, gray- white matter junction, vasculopathy
Influenza virus (Fig.4)	Acute necrotising encephalopathy - diffuse brain edema, symmetric thalami, brainstem, cerebellum

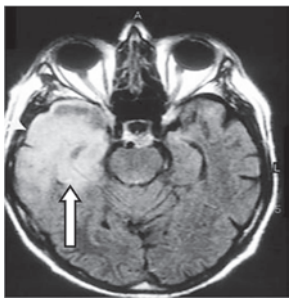

Fig.1. Axial MR FLAIR showing right temporal lobe involvement suggestive of HSV encephalitis

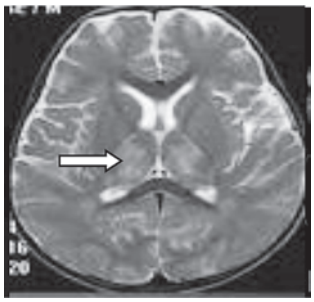

Fig.2. Axial T2 MR showing bilateral asymmetrical thalamic involvement in a child with JE encephalitis

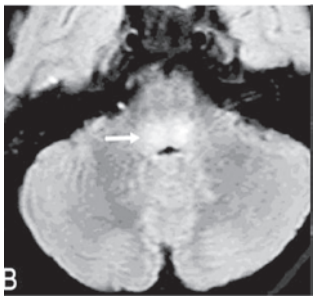

Fig.3. Axial FLAIR sequence showing posterior medulla involved in a child with entero virus encephalitis

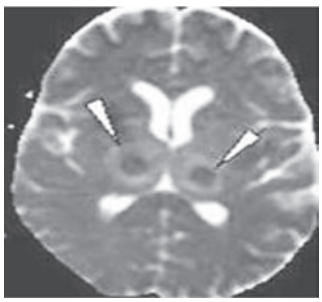

Fig.4.Axial T2MR showing bilateral symmetrical thalamic involvement with central areas of hemorrhage suggestive of acute necrotising encephalitis

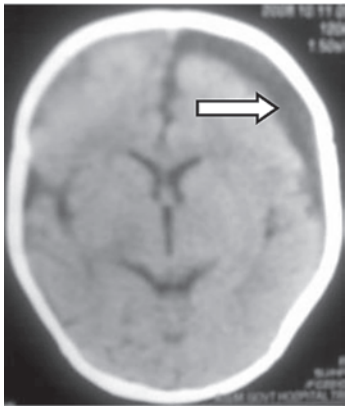

Fig.5. Plain CT brain - left frontal subdural effusion in bacterial meningitis

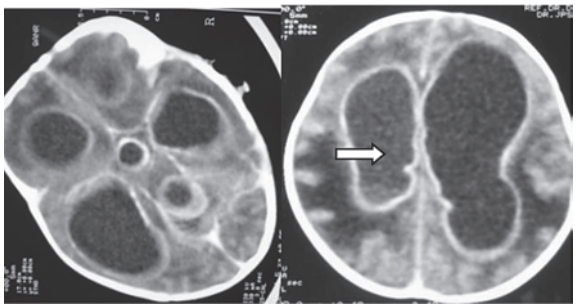

Fig.6&7. Contrast CT brain showing enhancement of ependymal lining of ventricles suggestive of ventriculitis

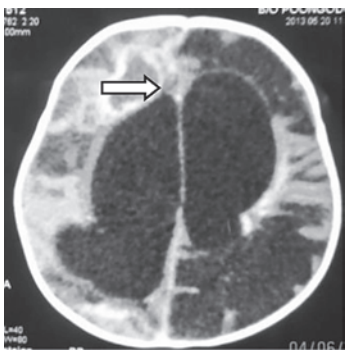

Fig.8. Contrast CT brain - Right frontal abscess with hydrocephalus

Tuberculous meningitis: Neuroimaging manifestations of tuberculous meningitis (TBM) include characteristic thick or nodular enhancement in the basal cisterns, although this finding may also be noted in meningitis due to other granulomatous (fungus or sarcoid) and neoplastic (carcinoma or lymphoma) disorders. Other possible sequelae of tuberculous meningitis such as infarcts, hydrocephalus, tuberculomas may be visualized.[8] The triad characterized by basal meningeal enhancement, hydrocephalus (Fig.9) and deep infarcts is highly suggestive of tuberculous meningitis.[9]

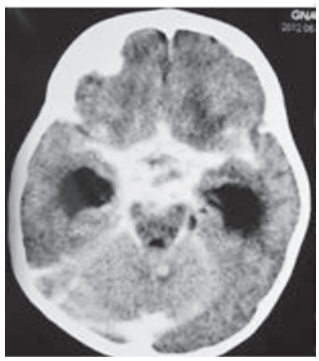

Fig.9. Contrast CT brain showing thick basal exudates and hydrocephalus in TBM

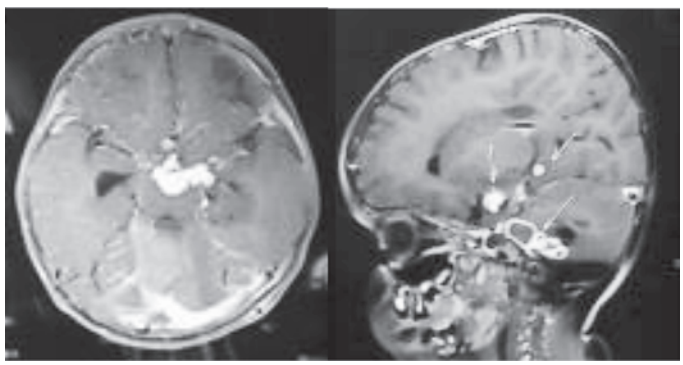

Fig.10. Post Gado contrast MR axial and sagittal views showing thick basal exudates, tuberculomas in interpeduncular region, pons and hydrocephalus

The characteristics of tuberculomas in MRI studies depend on whether they are caseous and the caseous matter has a solid or liquified center (Fig.10).[10,11] Non-caseous tuberculomas usually have a hypointense signal on T1 and a hyperintense signal on T2, with homogenous enhancement after gadolinium administration. Solid caseous granulomas have iso or hyposignal on both T1- and T2- weighted sequences.[12] Rajshekar, et al considered the differences between focal granulomatous lesions caused by cysticercosis and tuberculomas in individuals with seizures who have come from endemic regions and inferred that it would to be a difficult task without biopsy, but the occurrence of increased intracranial pressure and focal neurologic deficit, size greater than 2 cm, irregular outline and association with deviation of midline cerebral structures favor the possibility of tuberculoma.[13]

Tuberculomas are reported to demonstrate lipid peaks at 0.9 ppm, 1.3 ppm, 2.0 ppm and 2.8 ppm at MR spectroscopy and these peaks are believed to correlate with the presence of the high lipid content of the mycolic acid in the mycobacterial cell wall.

Neurocysticercosis

Radiographic appearance of neurocysticercosis mirrors the pathophysiologic stage of cyst degeneration. In vesicular stage, viable cysts show no surrounding edema or rim enhancement, however scolex may be seen (Fig.11). Visualisation of scolex in computed tomography or MR imaging is a strong evidence for neurocysticercosis. Colloid vesicular stage hydrocephalus shows ring like pattern of contrast enhancement with surrounding edema (Fig.12). The granular nodular stage begins with cyst retraction and formation of a granulomatous nodule and calcified nodular stage (Fig.13) is the last stage with gliosis and calcification.[14] Table II shows distinguishing features between tuberculoma and neuro cysticerosis.

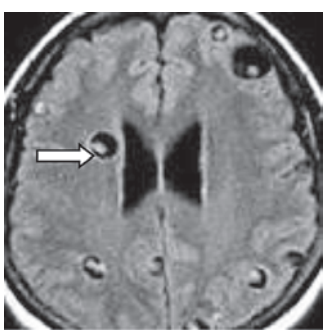

Fig.11.Axial MR FLAIR image shows multiple cysticerci in vesicular stage

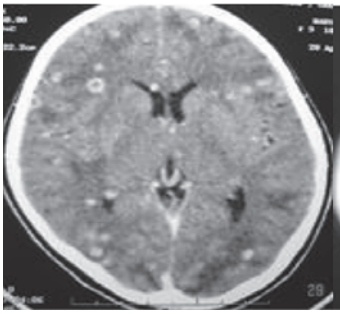

Fig.12. Contrast CT showing ring enhancing and disc enhancing lesions with surrounding edema

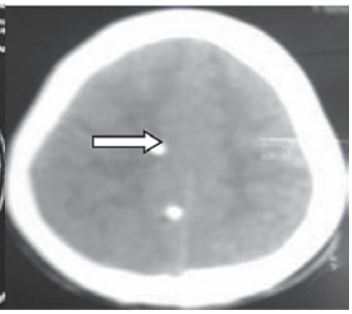

Fig.13. Plain CT showing calcified granulomas

Table II. Tuberculoma and neurocysticercosis - Distinguishing features in MRI

Tuberculoma	Neurocysticercosis
Size >20 mm	< 20mm
Irregular thick outline	Rounded thin outline
Marked perilesional edema	Less surrounding edema
Infratentorial or supratentorial	Predominantly supratentorial
Midline shift more likely	Midline shift less likely
Hypointense core in T2W images	Hyperintense core, eccentric dot best seen in fluid attenuated inversion recovery (FLAIR) or diffusion weighted imaging (DWI)
Lipid peak present	Lipid peak absent

Neurocutaneous syndromes

Phakomatoses or neurocutaneous syndromes are a heterogeneous group of congenital disorders with variable degree of penetration, primarily involving structures derived from the embryological neuroectoderm (central nervous system and peripheral nerves). In addition, surface ectodermal structures like skin, eye and other systems may also be involved.[15] Various neurocutaneous syndromes and their imaging findings are depicted in Table III.

Developmental anomalies

Central nervous system anomalies represent one of the most frequently involved structures with an estimated incidence of 1 per 100 births.[16] Cortical malformations must

Table III. Neurocutaneous syndromes and their imaging findings

Neurocutaneous syndrome	MR imaging findings
Sturge -Weber syndrome (Fig.14)	CT - subcortical calcification usually in parieto occipital region - parenchymal volume loss MRI T1contrast - prominent leptomeningeal enhancement in affected area - due to congested internal cerebral veins called 'pial angiomatosis', resulting in venous congestive ischemia with infarction and obliteration of cerebral parenchyma - enlarged ipsilateral choroid plexus
Tuberous sclerosis (Fig.15,16)	Subependymal hamartomas-(88% calcified), high in T1 and iso to high in T2, cortical/subcortical tubers- high in T2 and low in T1, subependymal giant cell astrocytoma - heterogeneous intensity on T1, T2 with contrast enhancement near the foramen of Monro leading to obstruction and hydrocephalus
Neurofibromatosis type I (Fig.17)	Focal areas of signal intensity (FASI) or unidentified bright objects (UBO) in deep white matter and basal ganglia or corpus callosum, i.e. areas of T2/FLAIR hyperintensity with no contrast enhancement, optic nerve glioma or optic pathway glioma, sphenoid wing dysplasia
Neurofibromatosis type II (Fig.18)	Intracranial vestibular schwannoma, intracranial and spinal meningioma, intraspinal-intramedullary ependymoma

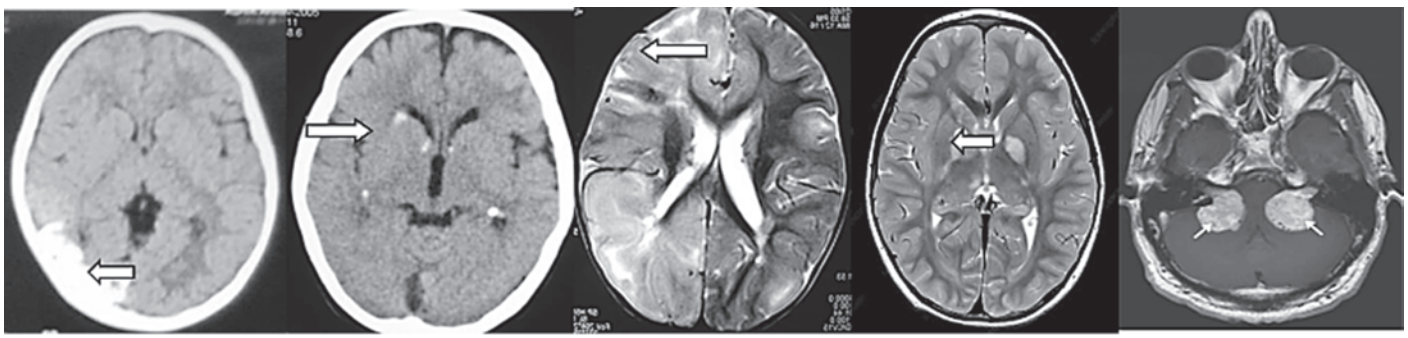

Fig.14. Plain CT shows calcified pial angioma in right parieto occipital region suggestive of Sturge Weber Syndrome

Fig.15. Plain CT brain shows subependymal calcified tubers in a child with tuberous sclerosis

Fig.16. Axial T2MR showing subependymal tubers and cortical tubers

Fig.17.Axial T2MR showing FASI in the basal ganglia in Neurofibromatosis type I

Fig.18.Axial MR FLAIR sequence showing bilateral acoustic neuromas in neurofibromatosis type II

be ruled out in essentially every pediatric patient with developmental delay or epilepsy. It is very difficult to make a diagnosis of congenital brain malformation based on clinical findings and use of CT or MRI is essential in these cases. Imaging findings in different developmental anomalies of central nervous system are described in Table IV.[17,18]

Inborn errors of metabolism

Neuroimaging is a particularly useful adjunct in the diagnosis of inborn errors of metabolism and should not be delayed until laboratory results are known, as it may provide early crucial clues to the diagnosis (Table V).[19,20]

Degenerative disorders - leucodystrophies

Magnetic resonance imaging has become the primary imaging modality in children with leukodystrophy and plays an important role in the identification, localization, and characterization of underlying white matter abnormalities in the affected patients. Systematic analysis of the finer details of involvement may help to narrow down the diagnosis (Table VI).[20]

Gray matter degenerative disorders

Generally imaging findings in gray matter degenerative disorders are nonspecific, usually diffuse

Table IV. Developmental anomalies of central nervous system - Imaging findings

Congenital malformation	Imaging findings
Dandy Walker malformation	Complete or partial vermian agenesis, cystic dilatation of fourth ventricle and enlargement of the posterior fossa with elevation of the transverse sinus, tentorium, and torcula
Arnold Chiari malformation (Fig.19-22)	Type 1 - Herniation of cerebellar tonsils into cervical canal - descent of >6 mm is abnormal Type 2 - Herniation of vermis, tonsils and medulla Myelomeningocele (nearly 100%) Type 3 - Type 2 + occipital encephalocele
Arachnoid cyst (Fig.23)	Extracerebral mass containing cerebrospinal fluid encircled by walls composed of arachnoid membrane
Callosal agenesis (Fig.24)	Complete callosal agenesis shows high riding third ventricle with spoke-like orientation of gyri around it, lateral ventricles widely separated, parallel and non-converging.
Joubert syndrome (Fig.25)	Small dysplastic or aplastic cerebellar vermis, prominent thickened elongated superior cerebellar peduncles giving characteristic molar tooth sign, key hole fourth ventricle
Lissencephaly (Fig.26)	No or few cerebral gyri and sulci Type I lissencephaly-typical figure eight configuration of brain with thickened cortex, flat broad gyri and shallow sylvian fissures Type II lissencephaly - thickened cortex having polymicrogyria
Schizencephaly (Fig.27-29)	Grey matter-lined cleft extending from the ependymal surface to pia mater, closed lip - cleft walls are in apposition, open lip - cleft walls are separated and filled with CSF
Heterotopia (Fig.30)	Presence of normal neurons at abnormal sites – nodular (common), band or laminar- a layer of neurons interposed between ventricle and cortex
Holoprosencephaly (Fig.31-34)	Alobar - single midline ventricle, absent interhemispheric fissure, falx cerebri, fused thalami and basal ganglia Semilobar - rudimentary occipital and temporal horns interhemispheric fissure - absent anteriorly thalami and basal ganglia partially separated Lobar - ventral portions of frontal lobes fused rudimentary frontal horns of lateral ventricles
Hemimegalencephaly (Fig.35)	Hamartomatous overgrowth of a part or all of one cerebral hemisphere

cortical atrophy. Specific findings may help us to narrow down the diagnosis in certain disorders (Table VII).

Demyelinating disorders

Magnetic resonance imaging plays an important role in the diagnosis, delineating the type, extent of demyelination and in the follow up of these disorders. Typical MRI findings in different types of demyelinating disorders are depicted in Table VIII.[21,22,23]

Stroke

Neuroimaging is essential for diagnosis and differentiation of stroke from stroke mimics such as hypoglycemia, demyelinating disorders, tumors, posterior reversible leukoencephalopathy syndrome and hemiplegic migraine. In general, the presence of diffusion restriction in the distribution of an arterial territory confirm stroke, although other entities such as brain tumors, abscesses, white matter diseases and seizures can exhibit reduced

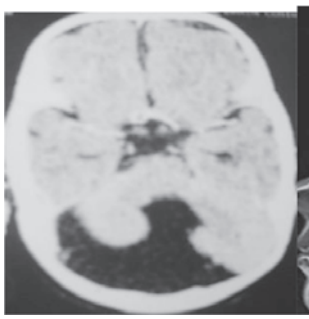

Fig.19. Plain CT brain showing Dandy Walker malformation

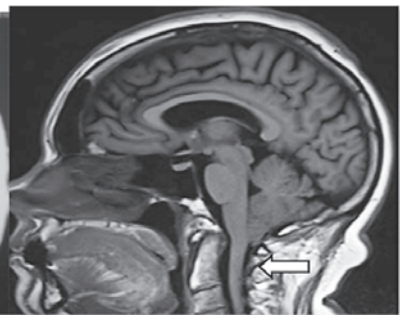

Fig.20. Sagittal T1 MR shows descent of cerebellar tonsils into cervical canal - Chiari I malformation

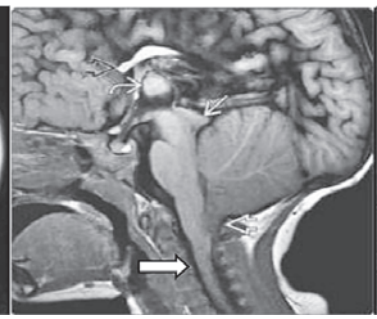

Fig.21. SagittalT1 MR showing descent of tonsils and medulla into cervical canal - Chiari II malformation

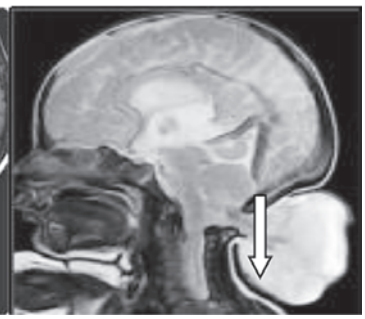

Fig.22.Sagittal T2 MR showing descent of medulla, tonsils with occipital encephalocoele - Chiari III malformation

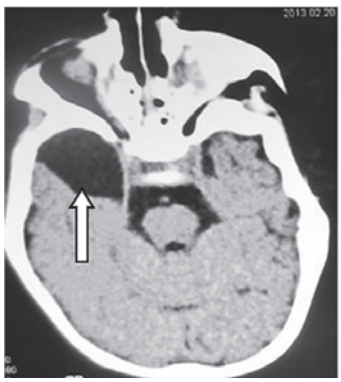

Fig.23. Plain CT brain showing arachnoid cyst in right temporal region

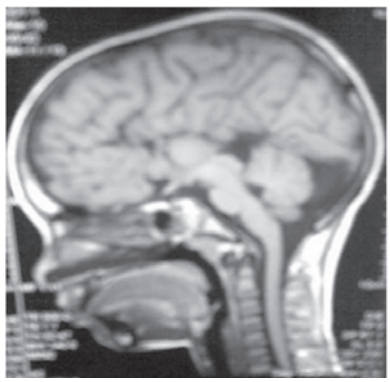

Fig.24. Sagittal T1 MR showing absence of corpus callosum

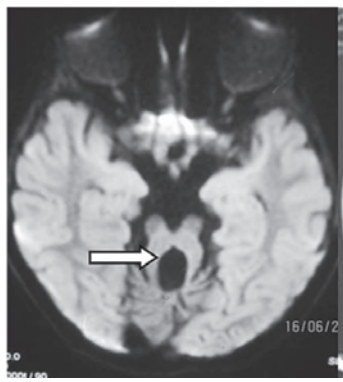

Fig.25. Axial MR FLAIR showing characteristic molar tooth sign suggestive of Joubert syndrome

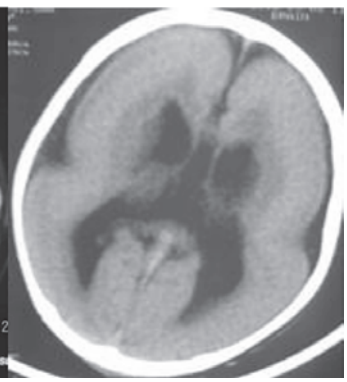

Fig.26. Plain CT brain showing smooth surface of brain with shallow sylvian fissure - figure of 8 appearance in Lissencephaly

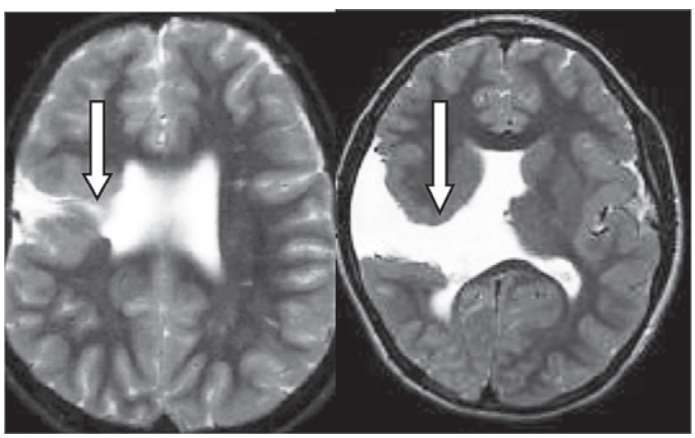

Fig.27. Axial T2 MR showing closed lip schizencephaly

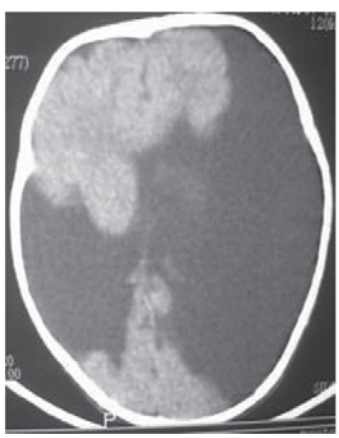

Fig.28. Axial T2 MR showing unilateral open lip schizencephaly

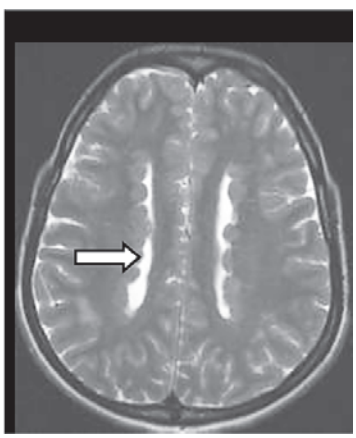

Fig.29. Plain CT brain showing bilateral schizencephaly

Fig.30. Axial T2MR showing nodular heterotopia

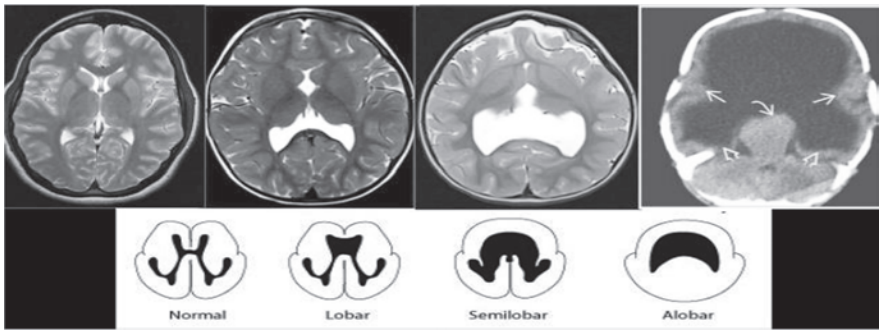

Fig. 31-34. Types of Holoprosencephaly

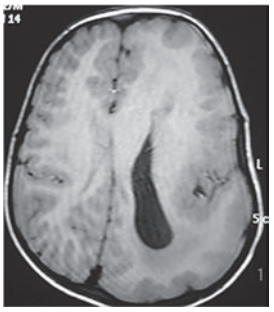

Fig.35. Axial T1 MR showing left hemimegalencephaly

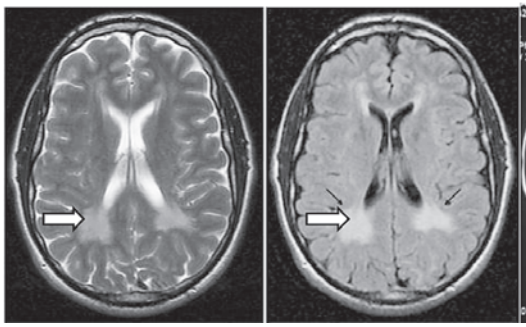

Fig.36(a & b).Phenyl ketonuria Axial T2 and FLAIR MR image shows periventricular white matter changes predominantly in parieto occipital region

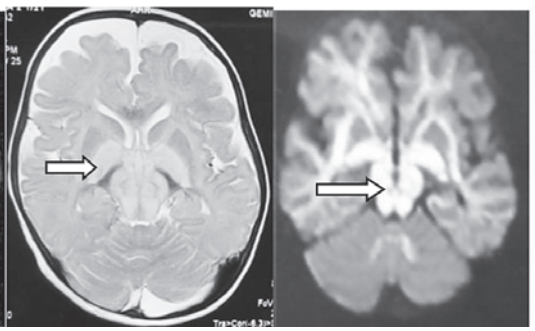

Fig.37(a & b).Maple syrup urine disease Axial T2 and DWI MR image showing high signal intensities in dorsal midbrain, cerebral peduncles and globi pallidi with diffusion restriction

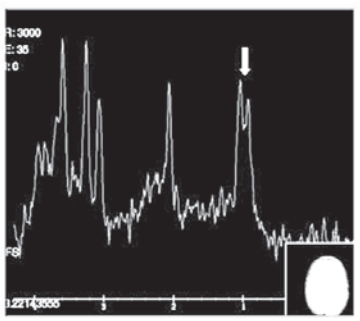

Fig.38.MR Spectroscopy abnormal wide peak at 0.9 ppm representing branched chain amino acids and keto acids

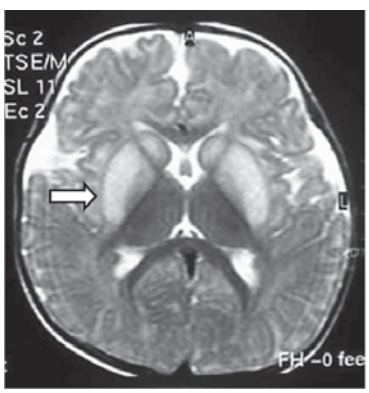

Fig.39. Methyl malonic acidemia Axial T2MR image shows bilateral symmetrical involvement of caudate and putamen

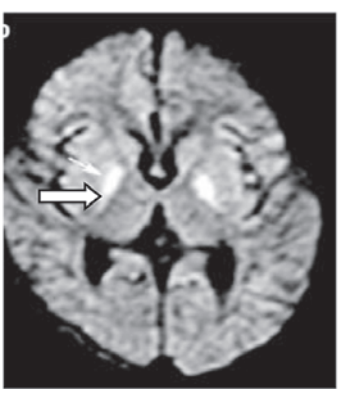

Fig.40.Propionic acidemia DWI showing diffusion restriction in both globus pallidi

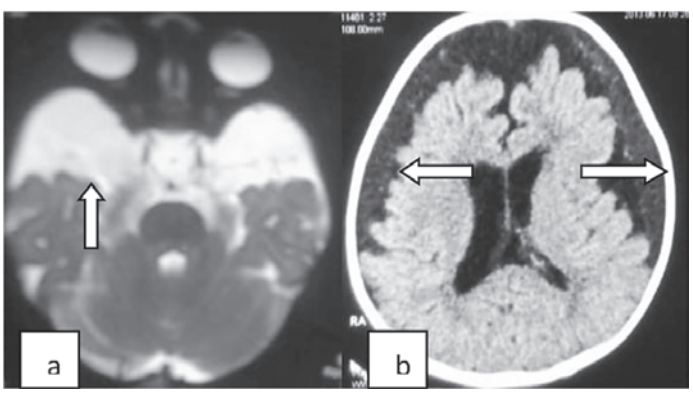

Fig.41a.Glutaric acidemia type I Axial T2MR image shows bats wing appearance

b. Axial FLAIR image showing bilateral chronic subdural hemorrhage in the same child

Table V. Important clues to diagnosis from neuroimaging in inborn errors of metabolism

Inborn error of metabolism	MRI findings	MRS findings
Phenyl ketonuria (Fig.36 a & b)	High signal intensities in periventricular/ parieto-occipital white matter	Phenylalanine peak at 7.37 ppm
Maple syrup urine disease (Fig.37 a & b / Fig.38)	Increased signal of cerebellar and perirolandic white matter, dorsal brainstem, cerebral peduncles, posterior limb of internal capsule,thalami and globi pallidi with diffusion restriction	Branched chain amino and ketoacids at 0.9 ppm
Methymalonic academia (Fig.39) Propionic academia (Fig.40)	Bilateral caudate and putamen,bilateral globi pallidi early - diffuse edemalate - hypomyelination, volume loss	
Glutaric aciduria type I (Fig.41a&b)	Bilateral fronto temporal atrophy, wide sylvian fissure - 'Bat wing' appearance, hilateral putamen involvement	
Nonketotic hyperglycinemia (Fig.42)	T2-hyperintense lesions of themyelinated white matter tracts, corpus callosal agenesis, vermian hypoplasia	Glycine peak at 3.5ppm
Sulfite oxidase deficiency (Fig.43)	Extensive cystic encephalomalacia	Sulfocysteine -3.6ppm Taurine - 3.4ppm Cysteine - 2.9 ppm
Creatine deficiency syndromes (Fig.44 a&b))	Normal	Absent or severely deficient creatine peak
Mitochondrial disorders (Fig.45 a, b & c)	T2-hyperintense lesions in dorsal midbrain, cerebral peduncles, pontine corticospinal tracts, dorsalmedulla, subcortical white matter with diffusion restriction	Lactate doublet at 1.33ppm

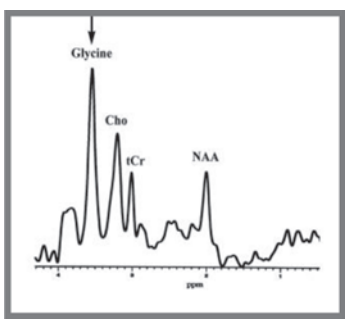

Fig.42. MR Spectroscopy showing elevated glycine peak in a neonate with non ketotic hyperglycinemia

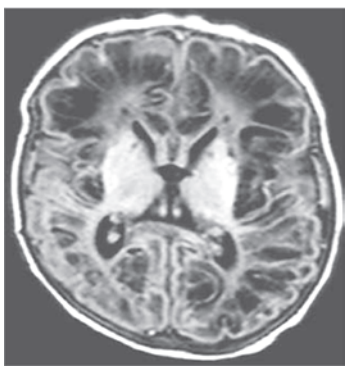

Fig.43. Sulfite oxidase deficiency Axial FLAIR MR image shows multicystic encephalo malacia

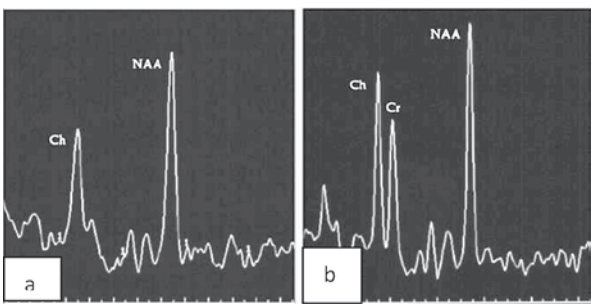

Fig.44a.Creatine deficiency disorder MR Spectroscopy showing absent creatine peak b. MR Spectroscopy in a normal child for comparison

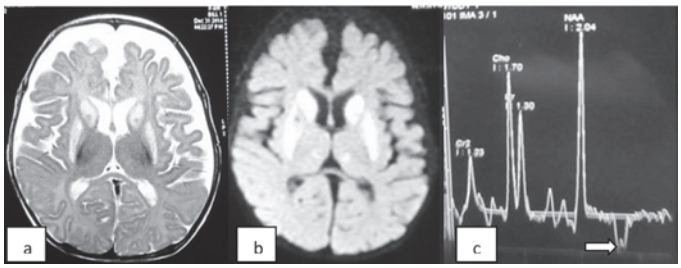

Fig.45a.Leighs encephalopathy Axial T2MR image showing bilateral symmetrical hyperintensities in basal ganglia

b.DWI showing diffusion restriction in the same areas and thalami

c.MR Spectroscopy showing inverted doublet lactate peak

Table VI. Leucodystrophies - Imaging findings

Disease	MRI findings	MRS findings
Metachromatic leucodystrophy (Fig.46 a & b)	Bilateral symmetric confluent areas of high signal intensity in the periventricular white matter with sparing of the subcortical U fibers. Tigroid or leopard skin pattern suggestive of sparing of the perivascular white matter seen. Corpus callosum, internal capsule, and corticospinal tracts, cerebellar white matter are frequently involved. No contrast enhancement.	
Krabbe disease (Fig.47 a & b)	Periventricular white matter in parieto occipital regions, thalami, corticospinal tracts, internal capsule, corona radiata, cerebellum may be involved. Optic nerve hypertrophy may be seen.	
Adrenoleucodystrophy (Fig.48 a & b)	Symmetric periventricular white matter in parieto occipital regions (peri-trigonal region), splenium of corpus callosum, cerebellar white matter. 3 zones- Inner zone - irreversible gliosis - markedly hyperintense at T2W. Intermediate zone- active inflammation- iso or hypointense in T2W and readily **enhances with contrast**. Outer zone - active demyelination moderately hyperintense at T2W.	
Alexander (Fig.49 a & b)	Extensive cerebral white matter involvement with frontal predominance, cavitations in white matter	
Canavan disease (Fig.50a & b)	Symmetric areas of homogeneous high signal intensity in T2W throughout the white matter including the subcortical U fibers, internal, external capsules, cerebellar white matter and globus pallidi.	marked elevation of NAA peak
Vanishing white matter disease (Fig.51)	Symmetric and diffuse white matter involvement with signal intensity which is close to, or similar to cerebrospinal fluid in every sequence.	Marked decrease or absence of NAA, creatine, choline peaks
Vander Knapp disease - Megalencephalic leukoencephalopathy with subcortical cysts (Fig.52)	Bilateral diffuse subcortical white matter involvement and subcortical cysts in anterior temporal lobes	

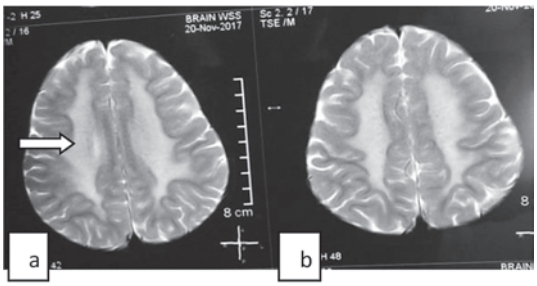

Fig.46a. Metachromatic leucodystrophy Axial T2 MR image showing bilateral symmetrical periventricular white matter hyperintensity. b. Tigroid pattern.

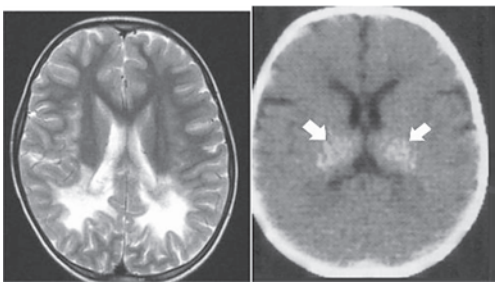

Fig.47a.Krabbe disease Axial T2 MR showing peri ventricular white matter hyperintensity

b. CT brain showing hyperdense thalami

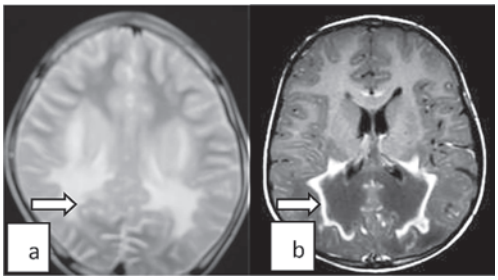

Fig.48a. Adreno leucodystrophy Axial T2 MR image shows symmetrical white matter hyperintensities in the parieto occipital region b. Axial T1 contrast showing contrast enhancement

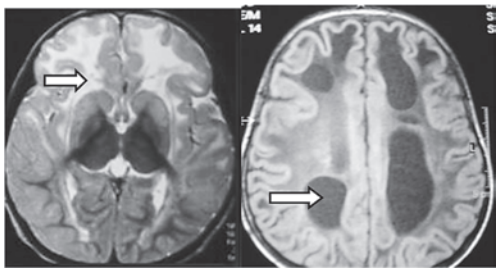

Fig.49a. Alexander disease Axial T2 MR showing frontal white matter involvement

b. Axial FLAIR showing cysts in the white matter

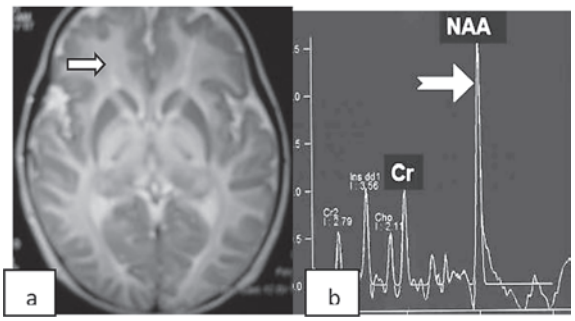

Fig.50a. Canavan disease Axial T2 MR image showing periventricular and subcortical white matter including U fibers and bilateral globus pallidi

b. MR Spectroscopy showing large NAA peak

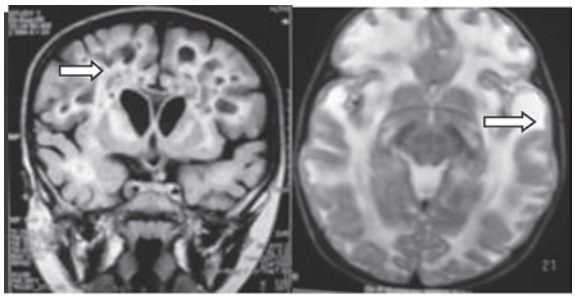

Fig.51.Vanishing White Matter disease Coronal FLAIR shows diffuse white matter involvement with cystic changes

Fig.52.Vander Knapp disease Axial T2 MR image showing diffuse white matter involvement with cyst in the anterior temporal pole

diffusivity (Fig.60 a & b). MRA of the head and neck is most often warranted to evaluate for transient cerebral arteriopathy (TCA), arterial dissection, moyamoya disease (Fig.61) and fibromuscular dysplasia.[24] In a child who is medically unstable, CT with CT angiogram (CTA) of the head and neck may be preferable. Repeat imaging may be performed to assess hemorrhagic transformation, infarct extension, mass effect, herniation, and stroke recurrence. Follow-up imaging is often performed between six weeks and three months to evaluate for progression or improvement of existing arteriopathies.[25]

Table VII. Diagnostic imaging findings in certain gray matter disorders

Gray matter disorder	MRI findings
Neuronal ceroid lipofuscinosis (Fig.53)	Diffuse cerebral and cerebellar atrophy
Mucopolysaccharidoses (Fig.54)	Prominent perivascular spaces, periventricular white matter involvement, cord compression in cranio cervical region
Fucosidosis (Fig.55 a&b)	Bilateral pallidal hyperintense signaling on T1W images and hypointense signaling on T2 W images
Panthothenate kinase associated neurodegeneration (PKAN) (Fig.56)	"Eye of the tiger"sign - central T2 hyperintense spot within the hypointense globi pallidi due to gliosis and vacuolisation in T2W images
Wilson disease (Fig.57)	Hyperintensity involving globus pallidi, putamen , caudate, thalami. “Face of the giant panda” sign in the midbrain with high signal in tegmentum and normal red nuclei

Table VIII. Neuro imaging findings in demyelinating disorders

Disease	MRI findings
Acute disseminated encephalo myelitis (ADEM) (Fig.58 a & b)	Bilateral, asymmetric, multiple poorly demarcated lesions in deep and subcortical white matter, (thalami and basal ganglia frequently affected) number of lesions varies with size ranging from <5 mm to 5 cm, in large confluent intramedullary lesions in spinal cord that extend over multiple segments are common. The degree of contrast enhancement is variable.
Multiple sclerosis (MS) (Fig.59 a & b)	Multiple well-demarcated lesions in the periventricular, juxtacortical, infratentorial, and spinal cord white matter. T1-weighted sequences may reveal "black holes" that represent complete tissue loss resulting from a previous inflammatory event
Neuromyelitis optica (NMO)	Bilateral optic nerve involvement and extension of T2 hyperintense signal posteriorly as far as chiasm, involvement of periaqueductal grey, hypothalamus, dorsal pons, medulla,corpus callosum, High T2 signal spanning at least three vertebral segments, often many more (known as a longitudinally extensive spinal cord lesion), cord swelling usually present in acute phase
Myelin oligodendrocyte glycoprotein (MOG) associated demyelination	Bilateral or recurrent optic neuritis sparing the optic chiasm, longitudinally extensive transverse myelitis involving lumbar segment and conus medullaris

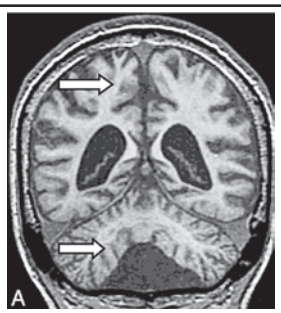

Fig.53. Neuronal ceroid lipofuscinosis Coronal T1 MR showing diffuse cerebral and cerebellar atrophy

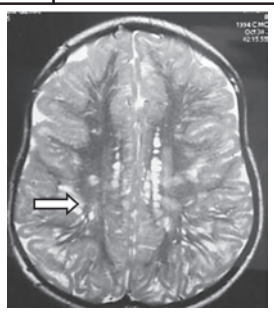

Fig.54.MPS Axial T2 MR showing prominent peri vascular spaces (Virchow Robin spaces)

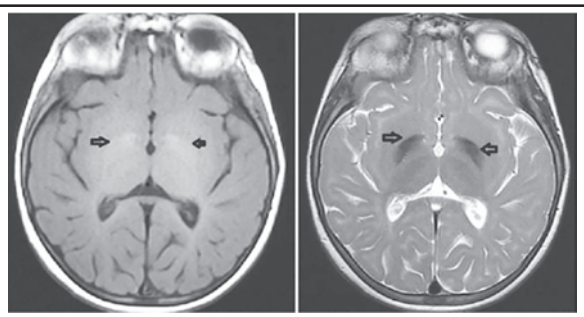

Fig.55a. Fucosidosis Axial T1 MR showing hyperintense globus pallidi

b. T2 MR showing hypointense globus pallidi characteristic

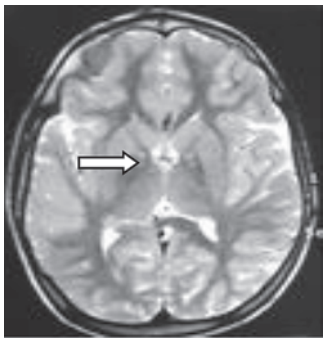

Fig.56. PKAN Axial T2 MR shows Eye of the tiger¨sign - central T2 hyperintense spot within the hypo intense globi pallidi

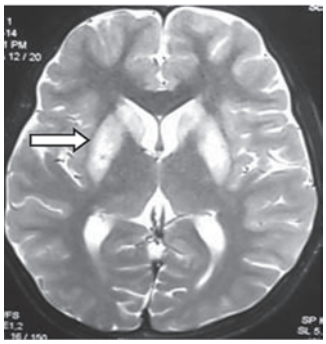

Fig.57. Wilson disease Axial T2 MR image shows hyperintense caudate and putamen

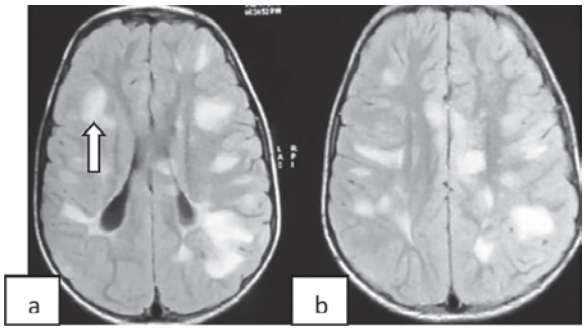

Fig.58 a & b. Acute disseminated encephalomyelitis Axial MR FLAIR sequences show bilateral, asymmetric, multiple hyperintense lesions in the deep and subcortical white matter

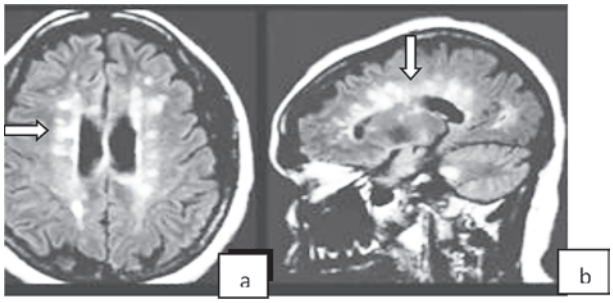

Fig.59 a & b. Axial and Coronal MR images showing multiple hyperintense lesions in periventricular white matter perpendicular to ventricular margins – Dawson's fingers. Involvement of corpus callosum seen in coronal picture

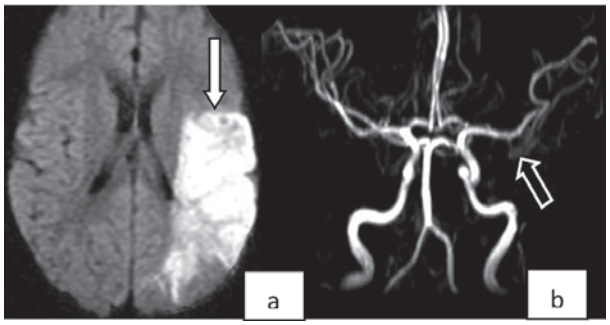

Fig.60 a & b. Axial DWI showing acute infarct in the left parietal region and MR Angiography showing focal irregularity of left middle cerebral artery

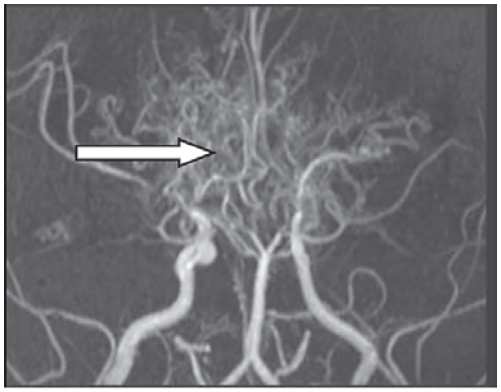

Fig.61.Moya Moya disease MR Angiography depicting occlusion of distal ICA and proximal MCAs bilaterally with collaterals with typical appearance of "puff of smoke"

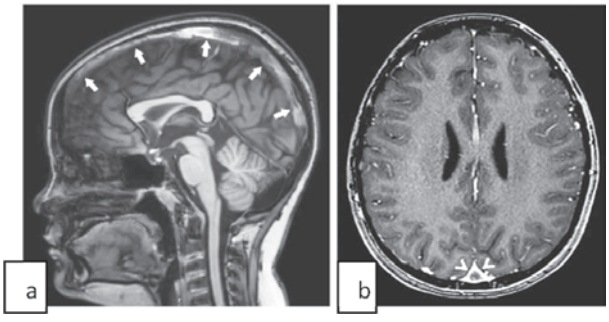

Fig 62.a.Superior sagittal sinus thrombosis. Sagittal T1 MR image showing abnormal hyperintense signal in the superior sagittal sinus

b. Axial contrast MR demonstrates the 'empty delta' sign of the superior sagittal sinus with contrast outlining a triangular thrombus

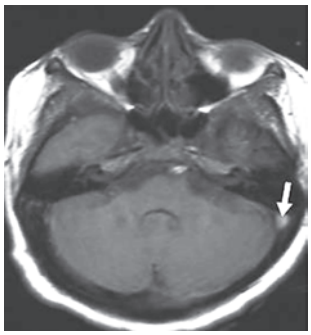

Fig.63. Sigmoid sinus thrombosis. Axial FLAIR MR image showing hyperintense signal at left sigmoid sinus

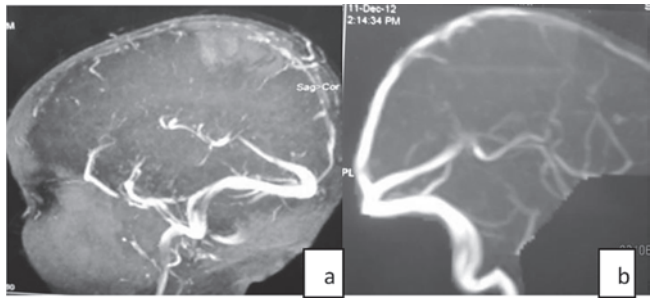

Fig.64a. MR Venogram shows thrombosis of superior sagittal sinus due to pyogenic meningitis. b. Partial recanalisation after three months

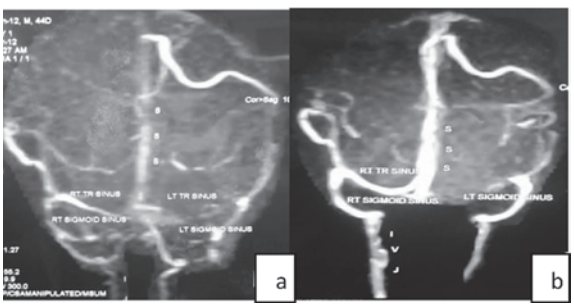

Fig.65a. MR Venogram shows thrombosis of superior sagittal, transverse, sigmoid sinuses in a child with protein C deficiency. b. Complete recanalisation of the sinuses after three months

Cerebral venous sinus thrombosis (CVST)

An ischemic infarction that crosses usual arterial boundaries particularly with a hemorrhagic component or in close proximity to a venous sinus is suggestive of CVST. Brain parenchymal changes in frontal, parietal and occipital lobes usually correspond to superior sagittal sinus thrombosis. Temporal lobe parenchymal changes correspond to transverse and sigmoid sinus thrombosis. Deep parenchymal abnormalities including thalamic hemorrhage, edema or intraventricular hemorrhage correspond to thrombosis of the vein of Galen or straight sinus.[26]

The primary sign of acute CVST on a noncontrast CT is hyperdensity of a cortical vein or dural sinus (Fig.62 a). Thrombosis of the posterior portion of the superior sagittal sinus may appear as a dense triangle, the dense or filled delta sign. Contrast-enhanced CT may show the classic "empty delta" sign, in which a central hypointensity due to very slow or absent flow within the sinus is surrounded by contrast enhancement in the surrounding triangular shape in the posterior aspect of the superior sagittal sinus (Fig.62 b). On CT, high hemoglobin concentration in the setting of dehydration or polycythemia can also be confused with clot, but in these individuals the entire vascular system is dense.[27]

MRI is more sensitive for the detection of CVST. MRI of the brain is suggestive of CVST by the absence of a fluid void signal in the sinus while T2 hypointensity is

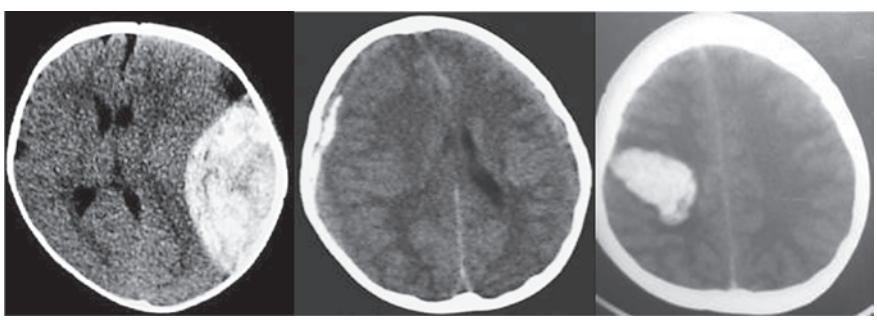

Fig.66a. Plain CT showing extradural hemorrhage (biconvex shaped) in the left parietal region with midline shift. b. Plain CT shows subdural hemorrhage (plano convex) in right parietal region with midline shift. c. Plain CT showing intra parenchymal bleed in the right parietal region

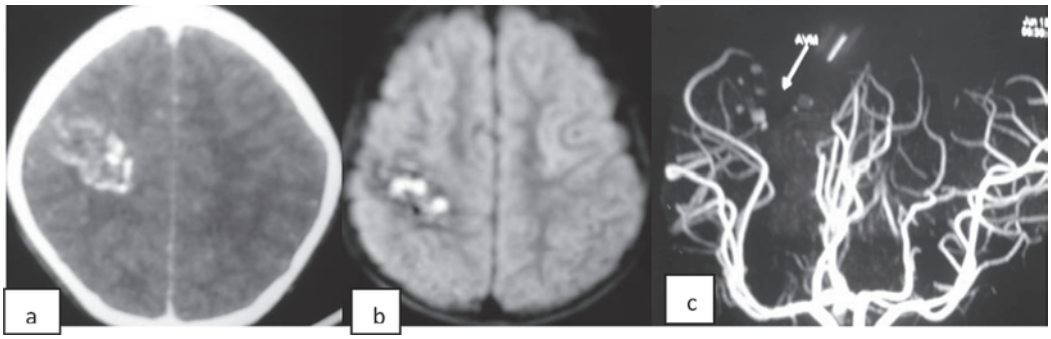

Fig.67a. Contrast CT showing enhancement of feeding vessels. b. Axial FLAIR image shows conglomeration of flow voids forming a "honeycomb" pattern. c. MR Angiography showing AVM

suggestive of a thrombus (Fig.63).[28] MRV shows non-visualization of occluded veins or sinuses due to absent signal and flow defect (Fig.64 a & b and 65a & b).[29]

A follow-up CT venography or MR venography at 3 to 6 months after diagnosis is reasonable to assess for recanalisation of the occluded cortical vein/sinuses.

CT is often the first neuroimaging modality performed because of its sensitivity for detecting hemorrhage, its short scan time and its availability in the emergency setting (Fig.66 a, b & c). If hematologic causes for hemorrhagic stroke are ruled out, CT angiography or MR angiography should be done to diagnose underlying arteriovenous malformations (AVM) or aneurysms. If no vascular malformation is noted during the acute period, repeat neuroimaging should be obtained after the hematoma has resolved because small vascular lesions can be compressed and concealed by the hematoma.

CT scan can demonstrate vascular calcifications associated with AVM. Contrast CT shows enhancement of the vascular channels (Fig.67a). MRI can demonstrate both dilated feeding arteries and enlarged draining veins. MRA can further delineate the anatomy and microarchitecture of an AVM (Fig.67 b, c).

Conclusion

Neuro imaging especially magnetic resonance imaging is a valuable tool in the hands of the clinician that helps in the diagnosis, management and follow up of neurological diseases in children.

Points to Remember

- ***Neuroimaging is an invaluable tool in the evaluation of neurological problems.***
- ***Cranial ultrasonography is the most frequently used neuroimaging modality in the perinatal period, particulary in the evaluation of hypoxic ischemic encephalopathy, subependymal- periventricular-intraventricular hemorrhage and hydrocephalus.***
- ***CT brain is the first imaging modality in unstable patients as it is widely available for emergencies, has shorter imaging time and lower cost. However, CT is generally suboptimal for imaging of structures in the posterior fossa and brain stem.***
- ***MRI is an indispensable tool in diverse CNS problems such as developmental anomalies, infections, neurocutaneous syndromes, demyelination and metabolic disorders.***
- ***Constraints with MRI are the need for sedation in young infants and its contraindication in the presence of metallic devices and implants.***
- ***MRA, MRV and MRS are additional facilities useful in identifying vascular and metabolic pathology.***

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CLIPPINGS

Corona viruses

Coronaviruses (CoVs) are a large family of enveloped, single stranded, zoonotic RNA viruses. They rapidly mutate and recombine leading to novel CoVs that can spread from animals to humans. The novel CoVs severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The 2019 novel coronavirus (SARS-CoV-2) is currently causing a severe outbreak of disease (termed COVID-19). This seem to less commonly affect children, cause fewer symptoms and less severe disease and are associated with much lower case-fatality rates in children.

Petra Zimmermann P., Nigel Curtis N. Coronavirus Infections in Children Including COVID-19 An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children.

NEUROLOGY

DIAGNOSTIC NEUROPHYSIOLOGY IN CHILDREN

Lakshminarayanan Kannan

Abstract: *Neurophysiological tests are an extension of the clinical examination and should be interpreted in the overall clinical context. In children they are often misinterpreted due to lack of experience. Normal EEG does not rule out epilepsy and an abnormal EEG per se is not diagnostic of epilepsy. EEG is not a confirmatory test but rather supports clinical diagnosis of epilepsy. Routine interictal EEG does not distinguish between epilepsy and epilepsy mimics. Nerve conduction study and needle electromyography are performed infrequently in the current era of genetic diagnosis.*

Keywords: *Pediatric electroencephalogram, Video-electroencephalogram, Electroencephalogram in pediatric intensive care unit, Electromyography.*

Commonly performed neurophysiological investigations in children are Electroencephalogram (EEG), nerve conduction study (NCS), needle electromyography (EMG), brainstem evoked response audiometry (BERA) and visual evoked potential (VEP). It is essential for the practicing pediatrician to understand the common indications, clinical use, interpretation of findings and appropriate management. Though neurophysiology tests are performed similarly across age groups, it is technically challenging to perform these investigations in young and uncooperative children who may need sedation.

Electroencephalogram

Electroencephalogram (EEG) is the most common clinical investigation ordered in children with neurological diseases. In this article the common indications, myths about EEG, technicality of EEG recording, pitfalls in interpretation, common EEG findings and clinical utility will be discussed.

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Indications for EEG[1]

Common indications for ordering EEGs are enumerated in Box 1. Judicious use of EEGs avoids unnecessary sedation, undue anxiety for the family and avoids overtreatment with antiepileptic medications. Clinical condition of the child as a whole should be taken into consideration for treatment decisions rather than just an abnormal EEG report.

Most important indication for EEG is to support the clinical diagnosis of epilepsy. EEG is not a confirmatory test. Thus, the diagnosis of seizures and epilepsy is purely clinical, based on detailed history of the reported episodes from first hand witnesses and review of home videos.

The next common indication is to classify epilepsy into focal or generalized. This dichotomous classification of epilepsy has crucial implications for the diagnostic and treatment approach. Interictal EEG epileptiform patterns often guide in choosing the most appropriate and effective antiepileptic drug (AED) for the given patient.

EEG provides crucial prognostic information. In cases of childhood absence epilepsy or benign Rolandic epilepsy, the electroclinical syndromic diagnosis allays parental

Box 1. Indications for EEG[1]

- Support of clinical diagnosis of epilepsy
- Classification of epilepsy into focal or generalized epilepsy
- Diagnosis of specific electro-clinical epilepsy syndrome (e.g., West syndrome)
- Prognostication (recurrence risk, remission rate, etc.)
- Ascertaining recurrence risk before AED withdrawal
- Evaluation of first afebrile seizure
- Exclusion of non-convulsive status epilepticus in cases of coma
- Investigation of acute febrile encephalopathy
- Unexplained encephalopathy, global development delay, language regression / acquired aphasia / auditory agnosia

anxiety as well as avoids investigations such as MRI brain, metabolic work up, CSF analysis and muscle biopsy.

There is no role for serial follow-up EEGs to monitor epilepsy. Exceptions include childhood or juvenile absence epilepsy, continuous spike-wave in slow wave sleep (CSWS) syndrome or Landau-Kleffner syndrome where complete resolution or significant improvement in EEG abnormalities mark the treatment endpoint. In these conditions it is desirable to get an EEG before withdrawal of AEDs, as the EEG patterns predict recurrence risk.

There is no role for EEG in febrile seizures including both simple and complex febrile seizures (Box 2). This is because, febrile seizures are benign and self-limiting in the long run, risks of prophylactic AED treatment far outweigh the perceived benefits and the long-term risk of epilepsy is not altered by the prophylactic AEDs. Even though EEGs may show transient or persistent epileptiform abnormalities in some patients with febrile seizures, there is no evidence to support that the prophylactic AED prevents future epilepsy. Many patients undergoing EEGs after complex febrile seizures are treated with continuous sodium valproate prophylaxis because of EEG abnormalities. This practice exposes the developing brain to the deleterious effects of sodium valproate without added benefits.

Diagnosis of common seizure mimics like breath-holding spells, shuddering attacks, hypnic jerks and infantile self-stimulation behavior is purely clinical. Home video recordings of the habitual episodes will clinch the diagnosis. EEG should be avoided in these cases as these are not diagnosis of exclusion. Many infants with breath holding spells are treated with diazepam, levetiracetam or clobazam because their EEGs have been reported as abnormal. In children with autism who never had seizures, EEG is not indicated as the role of prophylactic AED treatment is unclear and debatable.

Box 2. EEGs are NOT indicated and should be avoided in the following situations

- Febrile seizures (simple and complex)
- Breath holding spells, shuddering attacks, infantile masturbation behavior
- Sleep myoclonus / Hypnic jerks (sleep start)*
- Autism without seizures
- Syncope, headache, dizziness, vertigo

**Benign myoclonic jerks, which occurs usually on falling asleep.*

Role of EEG in pediatric ICU[2]

The most common indication for EEG in PICU is to rule out non-convulsive status epilepticus especially in patients who do not regain consciousness after status epilepticus (Box 3). Continuous bedside EEG monitoring (with simultaneous video recording) is indicated in cases of super-refractory status epilepticus and to induce and monitor burst-suppression pattern in cases of therapeutic coma.[2] Though EEG is not required in all cases, it is used as an ancillary test in brain death, especially when apnea test could not be completed.

Most ICU EEGs show diffuse slowing. This diffuse slowing pattern is non-specific and is not helpful in etiological diagnosis. On the other hand, certain specific EEG patterns denote specific etiology (e.g., delta-brush pattern in autoimmune encephalitis, periodic lateralized epileptiform discharges (PLEDs) in focal encephalitis or focal infarct, etc.)

Role of EEG in neonatal ICU

Continuous bedside EEG monitoring is increasingly being used in neonatal ICUs to manage patients with hypoxic ischemic encephalopathy, patients on therapeutic hypothermia and patients with recurrent seizures and metabolic encephalopathy (Box 4). Electro clinical dissociation is a common feature in neonatal seizures. This means that electrographic seizures could be silent clinically or clinical seizures may not show ictal EEG correlates. Only a third of neonatal EEG seizures manifest clinically. There is emerging evidence to show that treating subclinical seizures might improve long term neurodevelopmental outcome. In neonatal seizures, normal EEG predicts normal long term outcome whereas burst suppression pattern denotes poor long term outcome.

Box 3. Role of EEG in Pediatric ICU[2]

To

- rule out non convulsive status epilepticus
- detect electrographic seizures in cases of super refractory status epilepticus
- induce burst suppression and to monitor therapeutic (thiopentone or midazolam) coma
- investigate encephalopathy (febrile or afebrile) of uncertain etiology
- use as an ancillary test in brain death when apnea test could not be completed

Box 4. Role of EEG in neonatal ICU

To

- assess the severity of neonatal encephalopathy
- provide prognostic information in neonatal encephalopathy
- monitor moderate to severe HIE on therapeutic hypothermia
- monitor patients with repeated neonatal seizures (to look for subclinical seizures)
- look for burst suppression pattern in neonatal metabolic disorders

Box 5. Why a normal EEG does NOT rule out epilepsy?

- Minority of patients with epilepsy never show epileptiform discharges even on long records
- Epileptiform abnormalities are intermittent and could be occasional – can be missed during the short recording (sampling error)
- Epileptiform abnormalities may be so localized in certain electrode channels which may not be included in the montage (e.g., midline electrodes)
- Low amplitude epileptiform discharges may be buried in the background activity
- Deep seated seizure focus may not show abnormalities on the scalp surface
- Inappropriate EEG filter settings falsely filter out the epileptiform activity or make it appear like a background rhythm

Myths about EEG

Most common myth about EEG is that a normal EEG excludes epilepsy. It is crucial to understand that a normal EEG does not exclude epilepsy for the reasons listed in Box 5.

Another common myth is that an interictal EEG distinguishes between seizures and seizure mimics. But this is not true. Ictal video-EEG recording of the habitual episodes make this distinction possible but not the interictal EEG.

It is best to record an EEG as soon as possible after a seizure. This is because the yield of the EEG is maximal closer to the episode, in most cases. There is no need to wait for a few weeks before ordering EEG.

Technical factors in recording and reporting EEG in children

Recording EEGs in children with development delay, autism, hyperactivity and other behavior problems can be quite challenging. Both the EEG technician and the parents need patience and perseverance to be successful. Yield of the EEG could be increased by following the simple steps (Box 6). Pre-requisites for getting a good quality EEG recording are listed in Box 7.

Box 6. How to increase the yield of EEG?

- Include sleep recording routinely in all EEGs
- Activation procedures like hyperventilation and photic stimulation
- Sleeping 1 hour later the previous night and waking early on the day of EEG, in older children
- Record EEGs for 40-60 minutes if no abnormalities are found in first 30 minutes

Box 7. Pre requisites for a good quality EEG recording and reporting

- Good quality EEG machine with adequate sampling rate
- Qualified and well-trained EEG technician familiar with pediatric EEG recordings
- Child friendly staff and EEG lab ambience
- Clear instructions given to parents before EEG appointment (clean dry hair without oil, do not skip routine medications, sleep deprivation if needed, etc.)
- Good skin preparation before applying electrodes
- All 21 electrodes applied according to the standard International 10-20 system[4]
- Good electrode contacts with skin to achieve low impedance
- Appropriate EEG montages used for recording
- Appropriate filter settings used
- Preferably simultaneous video is recorded to aid interpretation
- Supervised EEG recording and appropriate annotations by the technician
- EEG traces are read and interpreted in the computer system (not on paper print outs)
- Periodic training of reporting personnel (pediatric neurologists)

Box 8. Common errors in interpreting pediatric EEG

- High amplitude physiological waves (sleep transients) are mistaken as abnormal
- Benign EEG variants are misclassified as abnormal
- Sharply contoured waves are misinterpreted as abnormal

It is not practical to record EEG in patients' home setting, though many parents request for the same. Home recorded EEG tracings are poor in quality, as there is no grounding of the electrical appliances. Sleep EEG (either spontaneous or induced with Triclofos[3] or melatonin) is good enough for the clinical diagnostic purposes, in young children. Oral sedatives and AEDs do not affect the diagnostic yield of the EEG adversely. Bedside, EEG is recorded in the ICU or in the wards when the patient is sick to be shifted to the EEG laboratory.

Many abnormal EEG patterns are peculiar to children and interpretation differs significantly compared to adults. Ideally pediatric EEGs should be reported by the neurologists who are familiar and conversant with the pediatric EEGs to avoid misinterpretation (Box 8). Periodic training and re-orientation in reporting of pediatric EEGs is the way forward. Single most important pitfall is that the EEG interpretation is arbitrary and operator dependent. The complexity of the EEG wave forms makes the standardization of EEG reporting and interpretation difficult, if not impossible.

Abnormal EEG patterns

Abnormal EEG patterns could be classified into abnormalities of the background rhythms or transient abnormalities that are epileptiform or non-epileptiform.

Box 9. Background abnormalities

- Diffuse or generalized slowing of the background rhythms (e.g., encephalopathy of any etiology, encephalitis, etc.)
- Hemispheric slowing (e.g.,stroke, Rasmussen encephalitis, etc.)
- Polymorphic focal slowing (indicative of underlying focal structural pathology) or
- Rhythmic focal slowing (could be benign variant as in occipital intermittent rhythmic delta activity)
- Attenuation of faster rhythms (indicative of lytic lesions such as gliosis or porencephalic cyst)

EEG background abnormalities are mostly non-specific and are not indicative of epilepsy by themselves (Box 9). In most cases, the background EEG abnormalities are not indicative of underlying etiology.

Though diffuse slowing is mostly nonspecific, certain genetic syndromes show rhythmic delta activity on EEG (e.g., long runs of frontal predominant rhythmic 2-3 Hz delta activity in Rett syndrome and Angelman syndrome, long runs of bilateral paroxysmal high voltage slow waves with occasional spikes over the fronto-polar regions in ring chromosome 20 and posterior predominant rhythmic 4-6 Hz theta activity in Angelman syndrome, etc.).

On the other hand, inter-ictal epileptiform abnormality has high specificity (78-98%) for associated epilepsy, but has low sensitivity. Epileptiform abnormality can be generalized or focal. Many clinicians interpret that the inter-ictal epileptiform discharges per se are seizures themselves. This is not true as these are only "inter-ictal" abnormalities which are more prevalent in patients with epilepsy than those without.

In children, certain epileptiform abnormalities have "low association with seizures". This means, many children showing these epileptiform patterns on EEG, would never have had seizures in the past or will have seizures only rarely, if at all, in future. That is, not all the children with these patterns will have epilepsy. These EEG patterns include centro-temporal spikes, central spikes in children with developmental delay or cerebral palsy[5], stereotyped focal occipital spikes, and bursts of irregular generalized spikes only on falling asleep. Up to 2-6 % of normal school going children can show one of these epileptiform abnormalities as incidental findings.[6] Thus, abnormal EEG showing epileptiform activity per se is not diagnostic of epilepsy.

Box 10. Indications for short-term video-EEG

- To record ictal events that occur in a predictable manner (absence seizures on hyperventilation, epileptic spasms on waking from sleep, sleep myoclonus on falling asleep, benign neonatal sleep myoclonus, etc.)
- To record and characterize habitual episodes (occurring multiple times per day)
- To induce episodes by suggestion in cases of psychogenic non-epileptic attacks

Short-term video-EEG

Though simultaneous video recording is preferred in all routine EEGs, this may not be feasible. Short term video-EEG recordings are preferred when habitual episodes occur multiple times daily and could be recorded in a predictable manner (Box 10). Electro-clinical diagnosis of specific epilepsy syndrome is possible with video-EEG recording of ictal events. Whenever feasible, it is prudent to record infantile spasms in short-term video-EEG to confirm the diagnosis of West syndrome and to avoid misclassification. This is essential because finding hypsarrhythmia in inter-ictal EEG is arbitrary and operator dependent. Video-EEG is the gold standard to confirm psychogenic non-epileptic attacks.[7] Families get convinced of psychogenic non-epileptic attacks when demonstrated on video-EEG.

Long-term video-EEG[1, 7]

Any video-EEG that is recorded overnight or for more than 12 hours can be considered as long-term. Long-term video-EEGs are usually recorded in the inpatient settings (Box 11). Overnight video-EEG is recorded whenever the classification of epilepsy is uncertain even after serial routine out-patient EEGs. Nocturnal seizures can be differentiated from other paroxysmal nocturnal episodes with certainty when recorded in video-EEG.

Precise localization of seizure focus for presurgical evaluation requires recording of at least few habitual seizures in video-EEG. Anti-epileptic medication doses may be gradually reduced to record habitual seizures if the usual seizure frequency is less than few per week.

Detailed review of nerve conduction study, electromyography, BERA and VEP is outside the scope of this article. Hence, some essential clinical points and indications are discussed.

Box 11. Indications for long-term video-EEG[1, 7]

- When epilepsy classification is unclear (generalized vs focal epilepsy)
- When nature of the episodes is unclear (nocturnal seizure vs parasomnia)
- When precise localization of epileptic focus is desired (pre-surgical work up)
- When seizure load needs assessment (epileptic spasms, electrographic seizures)
- When overnight sleep record is desired (to look for spike load in well controlled juvenile absence epilepsy or juvenile myoclonic epilepsy to decide on cessation of medications)

Box 12. Indications for nerve conduction study[8]

- Guillain-Barre syndrome
- Chronic inflammatory polyradiculo-neuropathy
- Polyneuropathy in hereditary or acquired systemic diseases
- Hereditary motor sensory neuropathy
- Mononeuritis multiplex
- Brachial or lumbar plexopathy
- Foot drop, carpal tunnel syndrome, traumatic neuropathy
- Chemotherapy and other drug related neuropathy (subclinical/clinical)

Nerve conduction study

Nerve conduction study (NCS) and EMG are essentially an extension of the clinical examination. Clinicians need to provide the detailed clinical data and differential diagnoses to the neurologist interpreting these investigations to get the maximum yield. Ideally, it is desirable that the reporting neurologist examine the patient clinically before proceeding with the nerve conduction study and needle EMG as these investigations cannot be interpreted and reported in isolation. Common indications for nerve conduction study in children are given in Box 12.

Motor and sensory nerve conduction velocity, latencies and amplitude of the responses are measured. These parameters are compared with the counterparts in opposite limb. Age-specific nomogram is utilized as the parameters of NCS differ significantly as a function of age.[9] NCS parameters could be within normal limits in cases of Guillain Barre syndrome (GBS) early in the course of the disease and should be repeated 4-7 days later if GBS is strongly suspected. Absent or prolonged F wave latencies are the earliest finding in GBS. One important caveat is that F waves could be physiologically absent during sleep.

Needle EMG

Special EMG needle is inserted in different muscles to record spontaneous activity, to demonstrate the maximal volitional capacity and muscle recruitment pattern. Spontaneous activity like fasciculations are noted in neuropathic conditions and are indicative of ongoing

Box 13. Indications for needle EMG[8]

- To differentiate between neuropathy and myopathy
- Inflammatory muscle disease - juvenile dermatomyositis
- To localize level of lesion in brachial[10] or lumbar plexopathy
- Juvenile motor neuron disease
- To demonstrate myotonia

denervation. Ideally, EMG is performed while the child is awake and co-operative, to assess the maximum volitional activity and recruitment pattern. But children get frightened by the needle and the painful procedure. Only spontaneous muscle activity can be assessed while the child is asleep and sleep EMG is enough to demonstrate myotonia.

In the era of genetic molecular diagnosis, the indications for NCS and EMG are shrinking (Box 12 & 13). Thus, nerve conduction study and needle EMG are no longer performed in cases of suspected spinal muscular atrophy (SMA), muscular dystrophy (including DMD) and most other congenital neuro-muscular diseases, as the genetic testing is the first line investigation of choice. As far as possible, invasive, frightening and painful tests such as needle EMG should be avoided in children. In the same way, muscle biopsies are performed now-a-days only rarely, when the genetic panel is inconclusive or negative.

Brainstem evoked response audiometry

BERA should be performed at the age 1-3 months in high risk newborns who are preterm < 34 weeks, very low birth weight, who had neonatal sepsis with or without meningitis and hyperbilirubinemia (Box 14). BERA is an objective test and the patient co-operation is not necessary. BERA can be recorded under sedation or during natural sleep in young children. Multiple sound clicks stimuli at 40, 50, 60, 70, 80 dB are presented through a headset to the right or left ear, one ear at a time. The response is recorded through the recording electrode placed just behind the recording ear. There are five standard wave forms (I-V) noted in BERA.

Box 14. Indications for BERA

- Those who fail hearing screen (OAE, audiometry, etc.)
- Preterm< 34 weeks/very low birth weight infants
- Hyperbilirubinemia, neonatal sepsis and meningitis
- TORCH infection sequelae, hydrocephalus
- Meningoencephalitis
- Traumatic brain injury
- Speech delay, suspected hearing loss
- External ear and other head and neck malformations
- Genetic syndromes with hearing loss
- Family history of sensory-neural hearing loss

Presence or the absence of wave forms, latencies of each waveform and inter-waveform latencies are noted. In profound sensory-neural hearing loss, all waveforms may be absent completely. Oto-acoustic emissions (OAE) should be used as a routine screening tool at around age 3 months in all infants.[11] Those who fail OAE in one or both ears should undergo BERA for confirmation.

Visual evoked potential

Visual evoked potential (VEP) tests the integrity of visual pathway from the retina to the occipital cortex. Stimuli are presented either in the form of pattern (on/off or pattern reversal) or flash light.[12] Pattern VEP is preferred whenever the patient can co-operate and can sustain visual fixation in the central red dot. Flash VEP is less reliable and is used in young and uncooperative children who cannot sustain fixation. Recording VEP is highly technical. If the patient is not fixing properly on the target or not looking at the flashes, the recorded data is unreliable. Two recording electrodes are placed on the scalp, one over the occipital and another over the frontal midline. Two wave forms (N75 and P100) are noted. The latencies of these two waveforms have nomogram. If the latencies are more than two standard deviations it means that nerve conduction in the optic pathway is slower. Common indications for VEP are given in Box 15.

Box 15. Indications for VEP

- Suspected poor vision or vision loss, amblyopia
- Cortical visual impairment (parieto-occipital gliosis)
- To assess visual function of infants
- Bilateral cataract before surgery - for prognostication
- Optic neuropathy of any etiology
- Acute demyelination - to detect subclinical involvement of optic nerves[13]
- Suspected cases of functional visual loss (conversion or malingering)[13]

Points to Remember

- ***Epilepsy is a clinical diagnosis and EEG is not a confirmatory test.***
- ***Inter ictal EEG does not distinguish between seizures and seizure mimics.***
- ***Some epileptiform patterns in EEG have low association with seizures in children.***
- ***Video-EEG is the gold standard to confirm psychogenic non-epileptic attacks.***
- ***Genetic testing is the investigation of choice in suspected cases of muscular dystrophy or spinal muscular atrophy; nerve conduction and EMG do not add value in these conditions.***

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CLIPPINGS

Neutrophil Volume, conductivity and scatter (VCS) as a screening tool in neonatal sepsis.

The objective of this study was to establish changes in Neutrophil volume conductivity scatter (VCS) in neonatal sepsis and to determine appropriate cut off levels using receiver operating characteristic (ROC) curves. 304 children were studied with 144 children in sepsis group and 166 in no sepsis group. mean neutrophil volume (MNV) and volume distribution width (VDW) MNV and VDW had good sensitivity (95%, 82%) and specificity (86%, 74%) for diagnosis of sepsis. The authors have concluded that Neutrophil VCS parameters, especially MNV, can be incorporated with other sepsis screen parameters in diagnosis of neonatal sepsis.

Nesargi P, Niranjan HS, Bandiya P, Benakappa N. Neutrophil Volume, conductivity and scatter (VCS) as a screening tool in neonatal sepsis. Sci Rep 10, 4457 (2020). https://doi.org/10.1038/s41598-020-61434-z.

NEUROLOGY

GENETIC TESTING IN NEUROLOGICAL DISORDERS - RADIOGENOMICS

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Abstract: *"Radiogenomics" is a new emerging field which correlate imaging features with genotype of disease. It has potential to play an important role in medicine, particularly neuro-oncology, metabolic and neurodegenerative disorders. Genetic testing confirms the diagnosis, helps in prognostication, predicts the risk of recurrence. But selecting the right genetic test is of prime concern and is difficult. Radiological finding or radio phenotype is useful in selecting the genetic tests needed. Role of radiogenomics is bidirectional. It predicts genotype on the basis of radiological phenotype and vice versa. So it plays an important role in bridging the gap between phenotype and genotype. It will further help the clinician to go for targeted sequencing of the gene which will be cost effective and time saving. For example the pediatric tumours which are studied on the basis of radiogenomics are medulloblastoma and glioblastoma. New generation genomic sequencing is very useful in sequencing the DNA at faster rate and lower cost. Whole genome sequencing, whole exome sequencing, clinical exome sequencing and target gene panel sequencing are various tests which are available. Radiogenomics is an important tool to indicate the likely genotype and directs towards the right genetic investigation.*

Keywords: *Whole genome sequencing, Whole exome sequencing, Gene panel sequencing, Radio genomics.*

"Radiogenomics" is a new emerging field which correlates the imaging characteristics of a disease (radio phenotype), with its genetic or molecular features (genomics or genetic phenotypes). It has potential to play an important role in medicine. The 1990s marked the beginning of genetic evolution In field of neurology too, genetics has an important role to play. Radio genomics still has a long way ahead before it becomes usable in daily clinical practice. First, it requires standardisation of imaging protocols, including image acquisition and post-processing, as well as robust segmentation algorithms that require minimal operator input.[1,2] Most of the studies mentioned in the literature involve novel imaging techniques that specically interrogate aspects of underlying tumor biology and biochemical pathways which have great potential in neuro-oncology. Radiomics applies to advanced computational methods to automatically extract and analyze hundreds or thousands of quantitative imaging descriptors (radiomic features) from a tissue-of-interest on medical imaging data, thus earning the -omics suffix to describe the field.[3] In the current era of precision medicine, identification of genetic variation is of prime importance. Genetic testing confirms the diagnosis, helps in prognostication, predicts the risk of recurrence in patient and their relatives. Importance of genetics is well known, however selecting the right genetic test is of prime concern (Table I). In resource limited setting as ours, each investigation is planned carefully. Here comes the role of radiology. Radio genomics aims to predict genotype on the basis of radiological phenotype and vice versa. Thus it plays an important role in bridging the gap between phenotype and genotype.

Clinico-radiological phenotyping helps to answer the question "Which genetic test should I ask for?"

Field of radio genomics can be extended to metabolic neurodegenerative disorders which have good homogeneity in clinical, radiological and genetic domain.[4] It will further help the clinician to go for targeted sequencing of the gene which will be cost effective and time saving. For example the pediatric tumours which are studied on the basis of radio genomics are medulloblastoma and glioblastoma. The genetic traits underlying were IDH mutations and 1p/19q co deletion.[5] IDH protein or Isocitrate dehydrogenase (IDH) 1 and 2 are metabolic enzymes that are mutated in a wide range of blood and solid tumor cancers.

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Table I. Comparison of features of different genetic tests

	Karyotype	FISH	Microarray	DNA sequencing
Detects large deletions or duplications	Yes	Yes	Yes	-
Detects deletions or duplications in part of a chromosome	-	Yes	Yes	-
Detects small deletions or duplications	-	-	Yes	-
Detects translocations	Yes	-		-
Detects sequence changes and single gene mutations	-	-	-	Yes

We should be clear that growing popularity of next generation sequencing cannot undermine the importance of karyotyping and microarrays etc. genetic tests should be ordered only after narrowing down the differentials clinically.

Next generation genetic sequencing is a technological advance which enable sequencing of million base pairs of DNA at a faster rate and lower cost. Depending on the extent of genes covered, next generation sequencing offers following tests (Table II).

- Whole genome sequencing (WGS) : WGS covers all introns (non coding regions) and exones (coding regions) i.e. determines the complete DNA sequence of an organism's genome at a single time.
- Whole exome sequencing (WES): It is a genomic technique for sequencing all of the protein-coding regions of genes in a genome (Exons) - about 20,000 genes, in one single test.
- Clinical exome sequencing : This is a test for identifying disease-causing DNA variants within the 1% of the genome which codes for proteins (exons) or flanks the regions which code for proteins (splice junctions) about 5,000-6,000 genes.
- Target gene panel sequencing: These are useful tools for analyzing specific mutations in a given sample. E.g. Inborn errors of metabolism, immune deficiency, epilepsy.

Table II. Comparison of features of next generation sequencing tests

Next generation sequencing (NGS)			
	Clinical exome sequencing	**Whole exome sequencing**	**Whole Genome sequencing**
Coverage	5000-6000 clinically relevant genes	20,000 genes	Covers coding and non-coding regions of genome
Depth of coverage	High 100X	High 100X	Low 30X
Limitations	Restricted number of genes Cannot detect novel genes	Cannot detect variants outside the exonic regions	Complicated interpretation of data Very costly
Clinical Use	Clinical	Clinical	Currently mostly used in research setting
Ability to detect copy number variants (CNV)	Cannot detect	Cannot detect	May be analyzed to detect CNV

Note: Good phenotyping remains the corner stone of deciding the appropriate genetic test and increasing likelihood of a positive yield.

Facts to be remembered while requesting NGS

1. Is this the right test for the disorder? - e.g. Triplet repeats cannot be detected by NGS, southern blot is the technique used.
2. Is the required gene included? - If we do not know what we are looking for, NGS may not provide the answer
3. Depth and coverage of the gene - e.g. SMN gene has poor coverage by NGS
4. Yield and cost
5. Turnaround time
6. Interpretation - Interpretation becomes complicated when a number of variants are detected with inaccurate phenotype.

In pediatric neurology, imaging has emerged as an important aid in bridging the gap between phenotype and genotype. Imaging findings in certain disorders are specific for a particular genetic variation. There are others where imaging findings narrows down the differentials, but multiple genes are implicated. In the former, targeted gene sequencing can be done, however the latter requires gene panel testing. Role of radiogenomics is bidirectional. Phenotype can predict the genotype, as well as genotype helps to predict likely phenotype. A simplified way of classifying these disorders are[6]

a) Disorders with clinical, imaging and genetic homogeneity
b) Disorders resulting from different gene mutation but having similar clinical and imaging findings.
c) Disorders with different clinical and imaging findings, inspite of involvement of a same gene

Common neurological diseases in pediatric population with diagnostic imaging findings are discussed briefly.

1. Pantothenate kinase 2 (PANK2) associated neurodegeneration with brain iron accumulation (NBIA)

Gene involved is PANK2, which provides instructions for making an enzyme called pantothenate kinase 2

MRI brain reveals the presence of "Eye of tiger sign" which indicates PANK2 mutation (Fig.1). There is hypointensity in globus pallidi on T2 weighted images resulting from iron deposition. There is foci of T2 hyperintensity (superomedial aspect) of variable size present within the area of T2 hypointensity representing pallidal destruction.[7]

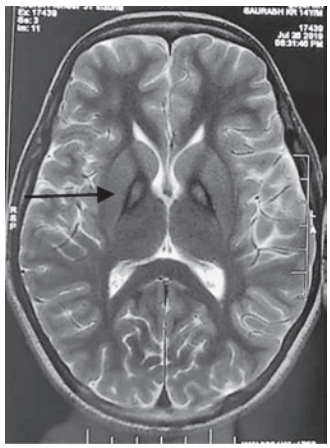


Fig.1. T2 weighted image - Eye of tiger sign. Hypointensity in globus pallidi with foci of hyperintensity medially (black arrow).

Differential diagnosis: Other disorders of neurodegeneration with brain iron accumulation (NBIAs) (non-PANK2) may also have globus pallidus T2 hypointensity but lack T2 hyperintense foci. All cases with PANK2 mutation have eye of tiger sign during course of illness but not all eye of tiger sign cases showed PANK2 mutation.

2. Infantile neuroaxonal degeneration

The gene is PLA2G6, which provides instructions for making an enzyme called A2 phospholipase.

MRI brain shows progressive cerebellar atrophy, vertically oriented splenium and claval hypertrophy. Some patients may show thinning of optic nerves and chiasma, and T2 hypointensity in the globipallidi (corresponding to iron deposition) (Fig.2).

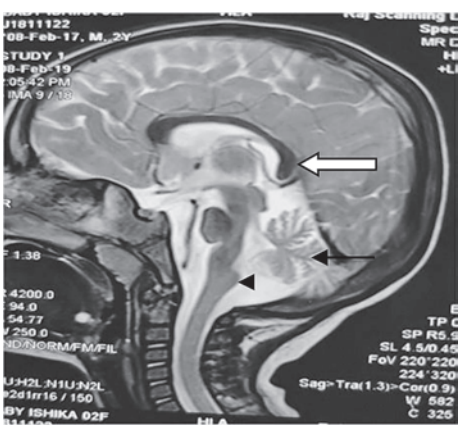


Fig.2. T2 weighted image shows cerebellar atrophy (black arrow), claval hypertrophy (black arrow head), vertically placed splenium (white arrow)

Differential diagnosis: Other NBIAs do not show cerebellar atrophy.

3. Megalencephalic leukoencephalopathy with subcortical cyst (MLC1)

The gene is MLC1 which encodes a membrane protein known as MLC1 which is found primarily in the brain. MRI shows swollen subcortical white matter. Subcortical cysts characteristically begin from anterior temporal lobes. It eventually involves frontal and parietal lobes too (Fig.3 a&b).

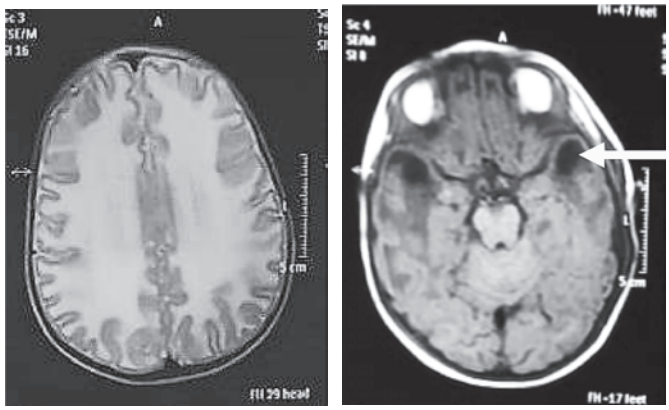


Fig.3. T2-weighted a&b MRI images of the brain show bilateral symmetrical diffuse white matter hyperintensity along with bilateral temporal cysts on FLAIR image.

4. Cerebral Adrenoleukodystrophy

The gene is ABCD1 (ATP binding cassette transporter) which provides instructions for producing the adrenoleukodystrophy protein (ALDP), which is located in the membranes of peroxisomes.

MRI findings: Most common pattern is predominant posterior white matter involvement. Usually first area to be affected is middle of corpus callosal splenium, extending into parieto-occipital areas. MRI shows T1 hypointensity and T2/FLAIR hyperintensity of affected white matter. There is characteristic contrast enhancement of inflammatory leading edge of demyelination (Fig.4).[8]

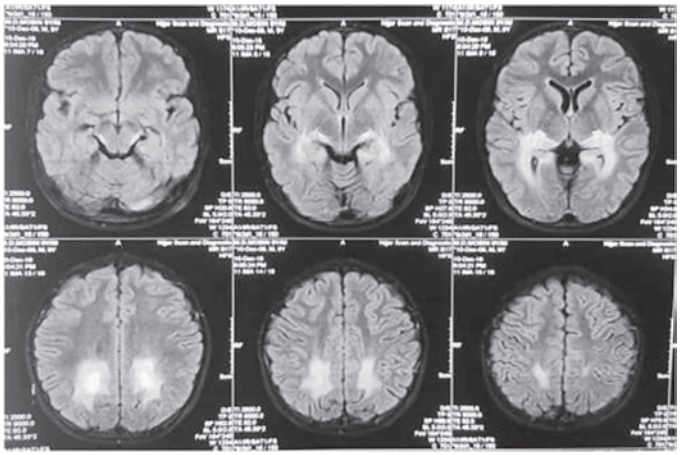


Fig.4. FLAIR images show Posterior predominant white matter involvement. Lowe score for this patient- 9-10.

5. Krabbe

The gene is GALC which encodes for an enzyme called galactocerebroside beta galactosidase (GALC)

CT scan shows high density in bilateral thalami, caudate nuclei, corona radiata, cerebellar dentate nuclei. MRI shows abnormally bright thalami on T1 weighted images. On T2 weighted images cerebellar nuclei, corticospinal tracts are abnormally hyperintense. Some also show enlarged optic nerves (Fig.5 a&b).[9]

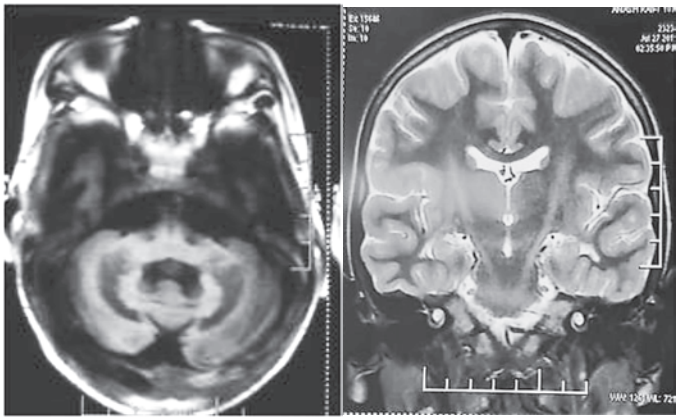


Fig.5 a&b. MRI image shows signal changes in bilateral dentate nuclei, Cortico-spinal tract involvement

6. Vanishing white matter

The gene is EIF2B, which encodes one of five subunits of eukaryotic translation initiation factor 2B.

MRI shows diffuse white matter signal changes. Abnormal hypointensity on T1, hyperintensity on T2.

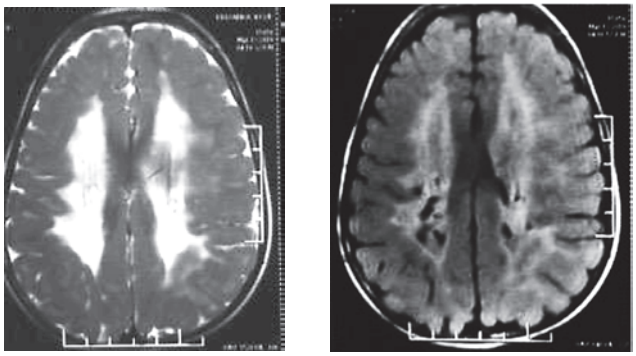


Fig.6. a&b. T2, FLAIR images show cavitating white matter involvement with sparing of subcortical white matter.

White matter eventually cavitates. On diffusion weighted images, diffusivity is reduced in areas which are in process of cavitation. Subcortical fibers may be spared early in the disease. Temporal lobes may be relatively spared (Fig.6 a&b).[10]

7. Alexander disease

The gene is GFAP, which encodes a protein called glial fibrillary acidic protein of mature astrocytes.

MRI changes: Frontal predominant cerebral white matter signal changes, periventricular rim with T1 hyperintensity and T2 hypointensity, abnormal signal changes in basal ganglia, thalami, brainstem is seen in MRI. Contrast enhancement is noted in periventricular region and lower brainstem regions (Fig.7).

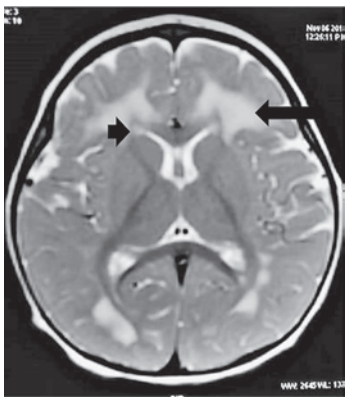


Fig.7. T2 weighted MRI image shows bilateral cerebral white matter hyperintensity predominantly in frontal lobes (long black arrow). In addition, there are focal ring-like lesions in frontal white matter at the tip of frontal horns (short black arrow).

8. Glutaric Aciduria I

The gene is GCDH, which provides instructions for making the enzyme glutaryl-CoA dehydrogenase.

MRI findings: Open sylvian fissures due to hypoplastic frontal and temporal opercula and T2/FLAIR hyperintensity in basal ganglia, delayed myelination is seen in MRI brain. During acute decompensation, cerebellum nuclei are involved. Chronic subdural hematoma is noted in few of the cases (Fig.8).[11]

9. Canavan disease

The gene is ASPA, which encodes an enzyme that catalyzes the conversion of N acetyl L aspartic acid (NAA) to aspartate and acetate.

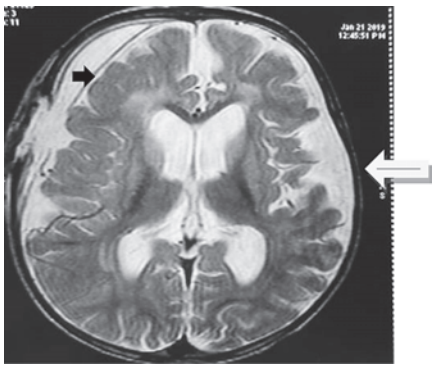


Fig.8. T2 weighted MRI image shows delayed myelination, abnormal signal change in bilateral basal ganglia, open sylvian fissures(white arrow) and subdural collection (black arrow).

MRI findings: MRI reveals T1 hypointensity and T2/FLAIR hyperintensity in the cerebral white matter. The subcortical white matter is affected early in the disease and appears swollen. Abnormal signal changes seen in corpus striatum, cerebellar dentate nuclei, dorsal pons, portions of cerebellar peduncles. Contrast enhancement is not reported. MR spectroscopy reveals elevated NAA peak (Fig.9).[12]

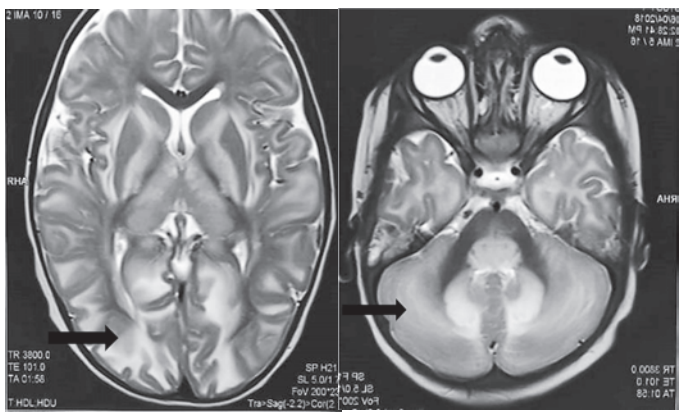


Fig.9. T2 weighted MRI images show hyperintensity in cerebral white matter, cerebellar dentate nuclei (Black arrows).

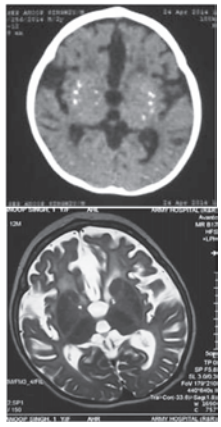
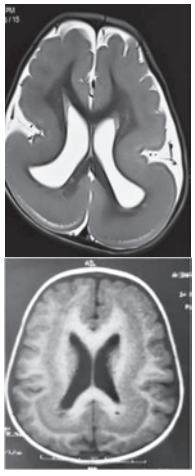
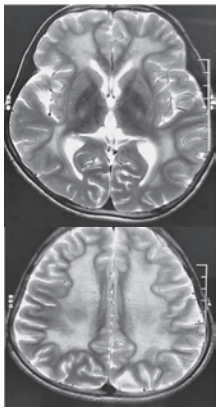
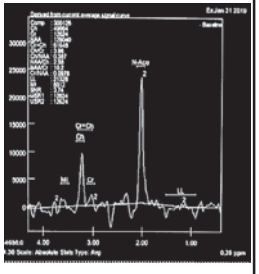
Others disorders which have characteristic imaging phenotype and reliably predicts the genotype are

1. L2 Hydroxy glutaric aciduria

The gene is L2HGDH, which encodes an enzyme called L-2-hydroxyglutarate dehydrogenase

MRI findings: Bilaterally symmetrical involvement of subcortical U fibres. Deep periventricular white matter, corpus callosum and internal capsule remain spared even

Table III. MRI features of few prototype conditions

Conditions	Genes	Radiology	Images
Aicardi-Goutieres Syndrome	TREX1, RNASEH2, RNASEH2C, RNASEH2A, SAMHD1, ADAR1	Punctate calcification especially in basal ganglia, white matter and/or dentate nuclei. White matter abnormalities, cerebral atrophy.	
Lissencephaly and subcortical band heterotropias	ARX, DCX, LIS1, RELN, TUBA1A, VLDLR	Brain surface appears smooth with absence (agyria) or abnormally wide gyri (pachygyria). Gyri typically ≥3 cm wide, cortex 10-15mm. Posterior to anterior or anterior to posterior gradient.	
Metachromatic leukodystrophy	ASA, PSAP	Abnormal signal changes in deep and periventricular white matter. Subcortical white matter is spared late in the course of disease. High resolution images show stripes of normal and affected myelin giving a tigroid pattern or leopard skin sign or stripe sign	
Creatine deficiency	GAMT, AGAT, SLC6A8	MRI is essentially normal in AGAT deficiency, GAMT deficiency shows bilateral T2 hyperintensity with reduced diffusivity in globi pallidi MR spectroscopy shows reduced or absent creatinine.	

in advanced cases. An anterior to posterior gradient can be observed. Basal ganglia is involved. Dentate nuclei is affected but cerebellar white matter and brainstem are spared. Vermis is significantly atrophied.[13]

Differential diagnosis: Canavan disease: Brainstem is involved and putamen and caudate nuclei are spared. Elevated NAA on MR spectroscopy.

2. Menke's disease

The gene is ATP7A, which provides instructions for making a protein that is important for regulating copper levels in the body.

MRI findings: Progressive brain atrophy, bilateral subdural hematoma, elongated and tortuous cerebral arteries. In absence of asphyxia or physical trauma these MRI findings are highly suggestive of Menkes.[14]

3. ACTA2 mutation

The gene is ACTA2, which encodes protein , smooth muscle actin that is involved in vascular contractility and blood pressure homeostasis.

MRI findings: Arterial ischemic stroke, MRA shows dilated proximal internal carotid artery (ICA), stenosis of terminal ICA, twig like abnormally straight intracranial arteries and absence of collaterals.[15]

4. Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)

The gene is DARS2, which encodes an enzyme called mitochondrial aspartyl-tRNA synthetase, which is important in the synthesis of proteins in mitochondria.

MRI findings: Signal abnormalities in cerebral white matter (subcortical white matter relatively spared), dorsal column and lateral cortico-spinal tracts in cervical spinal cord, medial medullary pyramids. Besides these signal changes may be seen in splenium of corpus callosum, internal capsule, superior and inferior cerebellar peduncles, trigeminal nerves and cerebellar white matter. On MR spectroscopy lactate can be elevated.[16]

Gene panel sequencing: There are number of other genetic neurological diseases where neuroimaging helps to narrow down the differentials. Some of these abnormalities can be caused by mutation in multiple genes. In these cases multiple gene panel where they are sequenced concomitantly at one step, is required rather than single gene targeted sequencing done one after another.[17]

Few of prototype disorders and their neuroimaging findings are mentioned in Table III.

In above mentioned conditions genetic diagnosis becomes important for therapeutic implication too. For example, all patients with creatine deficiency may not benefit with creatine supplement. Those with GAMT, AGAT deficiency show response however those with creatine transporter protein defect usually do not benefit from creatine supplement. Radiogenomics also helps to validate novel mutations as pathogenic by phenotypic categorization.[17] Thus it has a bidirectional role.

Conclusion

Radiogenomics is emerging as an important tool in the field of pediatric neurogenetics. It points out the likely genotype and directs towards the right genetic investigation. The radiogenomics has great potential to accelerate precision medicine, but it is still early in its evolution especially in pediatric neurological conditions apart from tumours. Optimum protocols for image acquisition and reconstruction must be identified and standardized, and robust protocol should be developed which should have excellent precision. Furthermore, databases need to be generated to incorporate imaging features with clinical and genetic data.

Points to Remember

- ***"Radiogenomics" is a new emerging field which correlates the imaging characteristics of a disease (radiophenotype), with its (genotype) genetic or molecular features.***
- ***Next generation genetic sequencing is a technological advance which enable sequencing of million base pairs of DNA at a faster rate and lower cost.***
- ***Whole genome sequencing, whole exome sequencing, clinical exome sequencing and target gene panel sequencing are various tests which are available.***
- ***Knowledge about the various features of these tests is essential to decide the specific test needed.***
- ***Good clinical phenotyping remains the corner stone of deciding the appropriate genetic test and increasing likelihood of a positive yield. But radiophenotype helps bridging the gap between clinical phenotype and genotype, by helping to select the type of genetic test is needed.***

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NEWS & NOTES

DRUG PROFILE

OXYGEN AS A PRESCRIPTION

***Jeeson C Unni**
****Ranjit Baby Joseph**

Abstract: *Oxygen is one of the most common life saving drugs widely used all over the world. It is often needed in many of the acute respiratory emergencies such as pneumonia and asthma where there is a risk of hypoxia. Long term oxygen therapy may be indicated in chronic respiratory conditions such as bronchopulmonary dysplasia (BPD), cystic fibrosis (CF), sleep disordered breathing, interstitial lung disease and pulmonary hypertension. Since medical grade oxygen is classified as a drug with specific biochemical and physiologic actions, with a distinct range of effective doses and well-defined adverse effects at high doses, oxygen needs to be prescribed like any other medication with specifications regarding dose, duration and method of delivery.*

Keywords: *Oxygen, Prescription, Delivery devices.*

In 1774, Joseph Priestley of England discovered the colorless, odorless, tasteless gas that Antoine Lavoisier later named oxygen.[1] It was not until 1934 that Dr Julius Hess, from Chicago, created the first inhaled oxygen delivery device for infants and young children which was an "oxygen box," that can be used within an incubator.[2] Further development and use of these delivery devices has resulted in significant health-care benefits, including a reduction in mortality. Today the administration of oxygen by inhalation continues to play an essential role in the survival of infants and children. However, it is one of the most misused drugs forgetting its toxic effects on lungs and neonatal retina.[3]

Oxygen is a drug and therefore must be prescribed only in life-threatening emergencies when it must be started immediately. Doctors should prescribe oxygen using target saturation range and sign the drug chart. Pulse oximetry should be available in all areas where oxygen is used and the oxygen saturation should be noted and documented prior to commencing oxygen. Suggested target saturation for most patients is 94-98%. However, patients at risk of hypercapnic respiratory failure have a lower target saturation range of 88-92%. Based on the clinical assessment of the patient, an appropriate delivery device and flow rate should be chosen and it should be adjusted to ensure that the patient's saturation is maintained within the target range using the lowest possible oxygen flow rate.[4]

All patients on oxygen therapy should have regular pulse oximetry measurements and the therapy should be decreased in stable patients with satisfactory oxygen saturations. Any changes to FiO_2 or flow rate must be documented, with corresponding respiratory assessment. When the oxygen is decreased, saturation should be monitored after 5-10 minutes, 30 minutes and 60 minutes or more to ensure that oxygen saturation remains within the desired range. When the amount of oxygen administered is changed and/or when oxygen saturation is recorded, the amount of oxygen the patient is receiving and the delivery device should be recorded in the clinical record. At each drug round the oxygen therapy being delivered to the patient must to be checked against the prescription. The current saturation, the delivery device and flow rate should be recorded in the case sheet.[5] In addition to the duration of use and oxygen flow, the prescription completed by the physician should define the delivery device (nasal cannula, mask, transtracheal catheter, etc.) and oxygen source (concentrator, liquid, compressed oxygen tanks, etc.)

Uses of oxygen in pediatrics

Oxygen, being the most common drug used in medical emergencies should be prescribed initially to achieve normal or near-normal oxygen saturation. In most acutely ill children with an expected or known normal or low arterial carbon dioxide ($PaCO_2$), oxygen saturation should be maintained above 92%; some clinicians may aim for a target of 94-98%. Hypercapnic respiratory failure is rare in children; in those children at risk, a lower oxygen saturation target of 88-92% is indicated.[6] In some clinical situations, such as carbon monoxide poisoning, hyperbaric oxygen therapy may be needed until the child is stable.[7]

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In certain conditions like pneumonia, pulmonary thromboembolism, pulmonary fibrosis, shock, severe trauma, sepsis, or anaphylaxis low arterial oxygen (PaO_2) is usually associated with low or normal arterial carbon dioxide ($PaCO_2$). Therefore there is little risk of hypoventilation and carbon dioxide retention, making high concentration oxygen therapy safe. In severe acute asthma, the $PaCO_2$ is usually subnormal but as asthma deteriorates it may rise steeply especially in children. These patients usually require high concentrations of oxygen and if the $PaCO_2$ remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently. Low concentration oxygen therapy is reserved for children at risk of hypercapnic respiratory failure, which is more likely in children with advanced cystic fibrosis or non-cystic fibrosis bronchiectasis, severe kyphoscoliosis or ankylosing spondylitis, severe lung scarring caused by tuberculosis, musculoskeletal disorders with respiratory weakness, an overdose of opioids, benzodiazepines or other drugs causing respiratory depression.[8] Oxygen therapy in neonates is a double edged sword and should be under expert supervision due to the risk of developing reactive oxygen species. Particular care is required in preterm neonates because of the risk of hyperoxia.[9]

Domiciliary oxygen therapy may be indicated in selected cases. It should be done only after careful evaluation by a respiratory care specialist. Special care should be taken to avoid smoking near the premises as there is always a risk of fire.[10] Long-term oxygen therapy may be necessary to maintain a target oxygen saturation of at least 92% in some children with bronchopulmonary dysplasia, primary or secondary pulmonary hypertension, sickle-cell disease with persistent nocturnal hypoxia, interstitial lung disease, cystic fibrosis, obstructive sleep apnoea syndrome, neuromuscular or skeletal disease requiring non-invasive ventilation.[11]

Use of oxygen in treatment of asthma: Nebulisations with beta-2 agonists are the drug of choice in the management of acute severe asthma. The nebulisations are to be administered over 5-10 minutes and should be driven by oxygen as these drugs can increase arterial hypoxemia due to ventilation perfusion mismatch. Most jet nebulisers require an optimum flow rate of 6-8 liters/minute and in hospital can be driven by piped air or oxygen. Domiciliary oxygen cylinders do not provide an adequate flow rate and therefore an electrical compressor is required for domiciliary use.[12]

Use of oxygen in management of anaphylaxis: Administering high-flow oxygen is part of the first line management of a child in anaphylactic shock. Angioedema is dangerous if laryngeal edema is present. In this circumstance adrenaline/epinephrine injection, oxygen, antihistamines and corticosteroids should be given as for management of anaphylaxis.[13]

Use of oxygen in treatment of status epilepticus: In all status epilepticus cases, initiation of oxygen is of prime importance to prevent hypoxic brain injury.[14]

Pain in sickle-cell disease: A mixture of nitrous oxide and oxygen may also be used with or without NSAIDS and/or opioids.[15]

Use in anesthesia: Volatile liquid anesthetics are administered using calibrated vaporisers, using air, oxygen, or nitrous oxide-oxygen mixtures as the carrier gas. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times. Higher concentrations of oxygen (greater than 30% - up to 50-60%) are usually required during inhalational anesthesia when nitrous oxide is being administered.[16]

Use in poisonings: Oxygen should be administered to children with cyanide poisoning and in carbon monoxide poisoning. The patient should be moved to fresh air, the airway cleared, and high-flow oxygen (100%) administered as soon as available.[17, 7]

Selection of oxygen delivery devices

Oxygen delivery method selected depends on age of the patient, oxygen requirements/therapeutic goals, patient tolerance to selected interface and humidification needs. In general, the delivery devices are classified into low flow systems and high flow systems. Low-flow systems include simple face mask, nasal prongs (low flow) and tracheostomy mask. High flow systems include non-re-breather face mask (mask with oxygen reservoir bag and one-way valves which aims to prevent/reduce room air entrainment), ventilators, CPAP/BiPaP drivers, face mask or tracheostomy mask used in conjunction with an Airvo2 humidifier and High Flow Nasal Cannula therapy (HFNC).[18]

All high flow systems require humidification. The type of humidification device selected will depend on the oxygen delivery system in use, and the patient's requirements. The humidifier should always be placed at a level below the patient's head. Indications for providing humidified oxygen are patients with thick copious secretions, non-invasive and invasive ventilation, high flow rate requirement with nasal prongs (>1L/min in neonates, >2L/min in children under 2 years, >4L/min in children over 2 years), facial mask flow rates of greater than 5 liters/minute and in patients with tracheostomy.[19]

Oxygen sources and flow regulators

Oxygen can be provided either from a wall source or from a cylinder. A wall source should provide at least 50 pounds per square inch (psi) of pressure at all times. Cylinders operate at psi of 1800-2400. Such high pressure cannot be directly delivered to the patient; hence a down regulating valve before a flow meter is required. A low flow system provides FiO2 that varies with patient's inspiratory flow rates. A high flow system provides fixed FiO2 at flows that meet or exceed patient's own inspiratory flow requirements. The flow requirement depends on minute ventilation (MV). Normal flow requirements are 3-4 times the MV and [MV= Tidal volume (Vt) x Respiratory rate (RR)]. The average Vt for a child is about 6ml/kg.[20]

Oxygen concentrators are devices that separate oxygen from nitrogen in the air by using adsorption and desorption over a material called zeolite that adsorbs only the nitrogen. No ventilator or CPAP machine can run on this as the outlet pressure is only 5psi. The resultant FiO_2 is about 0.4. This device may be used, if requirements permit, for home oxygen therapy.

Low flow nasal cannula

Oxygen is delivered through two soft prongs in the nostril. The prongs should have some space in the sides for exhalation. Humidification is not necessary. The flow is directed to the nasopharynx where humidification and the heat exchange takes place by natural nasal mechanisms. The maximum accepted flow is 2-4L/min. FiO_2 varies between 24-40% and it increases approximately 4% with each liter of oxygen. This is the preferred method of home oxygen therapy in infants.[21]

Though irritation and nasal obstruction may occur, nasal prongs are generally well tolerated. The indications are minimal oxygen requirements (<30%), weaning off from oxygen and chronic oxygen therapy on low concentrations. The advantages are comfort and conservation of the gas.

Simple face mask

It is useful for acute situations and short term use only (Set at 5-10L/min). O_2 flow must be set to a minimum of 5 Liters/min to facilitate clearance of CO_2. FiO_2 varies between 35-55%. It fits on patient's face without much discomfort and has perforations which are exhalation ports. The most appropriate size should be selected and care must be taken to avoid pressure points or eye damage. They can provide a maximum of 40% oxygen but this can vary with the flow rate. The disadvantage is that it is difficult to feed children requiring face mask and some children feel claustrophobic with its use.[22]

Oxyhood

Usually used for small babies and can deliver FiO_2 precisely. A clear transparent hood that ensures enough room for free neck and head movement is ideal. Every unit should maintain at least 3-4 sizes. Too big a hood will dilute the oxygen and too small a hood will cause discomfort and carbon dioxide accumulation. Oxygen gradients within the hood could vary as much as 20% from top to bottom. Fixed oxygen concentrations from 22 to 80% can be maintained with a minimum of 7-10 L/min oxygen flow. The hood has an outlet at the top to release the accumulating CO_2 that, being lighter than O_2, rises to the top. Although these devices theoretically deliver FiO_2 >0.5, they are best suited for patients who require <0.5 FiO_2.[23] There is no need for humidification; further, gastric distension and risk of airway obstruction by mucus are negligible.[24] The oxyhood is generally well tolerated. The disadvantages are the limitation on mobility (undesirable for prolonged oxygen therapy) and discontinuation of the enriched oxygen environment during feeding or suctioning.[25]

Non re-breather mask

Even though it is a low flow system it can work as a high flow system as it provides high FiO2. These are like masks but have a valve at the entry port that allows only oxygen from the source to enter the reservoir thus preventing re-breathing. It prevents room air from being entrained by an additional one way valve at the exhalation port. A well-fitting mask can provide up to 100% oxygen (Table I). When in doubt of the patient's requirements or if the patient is sick, as in the case of shock states, respiratory distress, cardiac failure, this is the mask to be chosen to

Table I. Oxygen percentages with different systems

Litres/min	Simple mask	Non re-breathing mask
5	40%	
6	45-50%	55-60%
8		60-80%
10		80-90%
12		90%
15		90-100%

institute oxygen therapy as it will provide maximum oxygen and build reserves, even prior to intubation. The oxygen flow should be set at a minimum of 10-15L/min (80-95% FiO_2).[26]

Venturi masks

These are high flow devices which allows precise measurement of oxygen delivered. Oxygen is delivered through a narrow orifice at a high flow based on Bernoulli principle. There are openings near the nozzle that allow room air to be sucked in, diluting the oxygen. Changing the size of the nozzle, the flow rates, as well as the ports, allows control of the amount of oxygen (Table II). This device guarantees fixed FiO_2 delivery and can save the oxygen costs as the high flow comes from the air at low oxygen concentrations. Increased rate of breathing does not affect the concentration of oxygen delivered. Each device will have a table on the package insert as a guide to flow rates required by that particular device.[27]

Continuous positive airway pressure (CPAP)

Continuous positive airway pressure (CPAP) is a type of positive airway pressure, where the airflow is introduced into the airways to maintain a continuous pressure to constantly stent the airways open, in people who are breathing spontaneously. It is indicated when the oxygen requirement is >60% with a PaO_2 of <60mm Hg. The background PEEP reduces the work of breathing, increases the FRC, recruits alveoli, increases static compliance and improves ventilation perfusion ratios. It maintains the set pressure throughout the respiratory cycle, during both inspiration and expiration and differs from bilevel positive airway pressure (BiPAP) where the pressure delivered differs based on whether the patient is inhaling or exhaling. These pressures are known as inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP).[28]

Table II. Venturi devices and delivery of oxygen

Litres/min (Oxygen / Total)	Oxygen concentration (percent)	Air: Oxygen ratio
2/53	24	25:1
4/45	28	10:1
6/47	31	7:1
8/45	35	5:1
10/33	40	3:1
12/32	50	5:3

In small neonates weighing <1400g, CPAP is best delivered using snug fitting nasal prongs. A pacifier may help in keeping the mouth snuggly closed. Various CPAP systems are available - the unit-made underwater seals and the more expensive bubble CPAP systems and ventilator systems. It could be tried prior to conventional ventilation in any spontaneously breathing patient who does not require emergency ventilation. Apart from nasal CPAP, other ways to provide CPAP are via nasopharyngeal tube or via face mask.[29]

High-flow nasal cannula

High flow nasal cannula (HFNC) oxygen delivery, also sometimes called heated humidified high flow nasal cannula (HHHFNC), is a relatively new non-invasive ventilation therapy that seems to be well tolerated in neonates and children with hypoxemic respiratory failure.[30] Before the advent of HFNC, clinicians were not comfortable administering a flow of >1 L/min via nasal cannula for newborns and >2 L/min in older children, due to the lack of adequate humidification.[31] The equipment includes traditional nasal cannula style prongs to deliver heated, humidified oxygen at flow rate starting at 1 L/kg/min that may be escalated to 2 L/kg/min based on work of breathing. An air-oxygen blender allows FIO_2 to be directly manipulated.[32]

Table III. Sample oxygen prescription

Name and hospital ID	Date and time
Current respiratory status	Respiratory rate Work of breathing Oxygen saturation
Target saturation range	
Reason to initiate oxygen support	
Mode of delivery	Nasal prongs Oxyhood Face mask Non re breather mask HFNC CPAP Mechanical ventilation
Flow rate and FiO_2	
Countersigning doctor and ID	

How to write an oxygen prescription

Since medical grade oxygen is classified as a drug, one needs to ensure that the prescription should detail: Patient information, drug (O_2), route (device), dose (flow/ FiO_2), target saturation, documentation and reason to start (Table III).

Contraindications to oxygen therapy

There are no absolute contraindications to oxygen therapy if indications are judged to be present. The goal of oxygen therapy is to achieve adequate tissue oxygenation using the lowest possible FiO_2. Some congenital heart defects can lead to an unbalanced circulation which may be made worse by administration of oxygen due to pulmonary vasodilation and subsequent systemic ischemia. This should be considered in a baby who presents unwell in the first two weeks of life with absent or weak femoral pulses and a heart murmur and is not improving with oxygen.[33] Supplemental O_2 should be administered with caution in patients suffering from paraquat poisoning and with acid inhalation or previous bleomycin lung injury.[34,35]

Cautions

In patients with chronic carbon dioxide retention, oxygen administration may cause further increases in carbon dioxide and respiratory acidosis.[36] Children with chronic neuromuscular disorders, chest wall deformities, cystic fibrosis, morbid obesity and chronic lung disease of prematurity are at risk. Evidence has also shown high concentration oxygen can cause a clinically significant increase in CO_2 in patients with severe exacerbations of asthma.[37] Other precautions/ hazards/ complications of oxygen therapy include drying of nasal and pharyngeal mucosa, oxygen toxicity, absorption atelectasis, skin irritation and fire hazard.[8]

Adverse effects

Dry or bloody nose, skin irritation around the nasal cannula or face mask, drowsiness, morning headaches and retinopathy of prematurity in newborn infants are common adverse effects due to injudicious administration of oxygen. Oxygen toxicity, caused by excessive or inappropriate supplemental oxygen, can cause severe damage to the lungs and other organ systems. High concentrations of oxygen, over a long period of time, can increase free radical formation, leading to damaged membranes, proteins and cell structures in the lungs. Prolonged high concentrations can be toxic to the pulmonary epithelium and hyperbaric oxygen can cause convulsions.[38]

Points to Remember

- ***Oxygen must be considered a medication that warrants a documented prescription before administration, except in emergency situations where written prescription is not mandatory to initiate the therapy***
- ***The prescription should include indication, target saturation range, mode of delivery and flow rate.***
- ***Choice of oxygen delivery device is based on clinical decision.***

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CLIPPINGS

Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults.

The clinical, laboratory, and chest CT features of 20 pediatric inpatients with confirmed COVID-19 infection were retrospectively analyzed during 23 January and 8 February 2020.

Procalcitonin elevation and consolidation with surrounding halo signs were common in pediatric patients which were different from adults. It is suggested that underlying coinfection may be more common in pediatrics, and the consolidation with surrounding halo sign which is considered as a typical sign in pediatric patients.

Wei Xia, Jianbo Shao, Yu Guo, Xuehua Peng, Zhen Li, Daoyu Hu. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatric Pulmonology 2020 March 5.

GENERAL ARTICLES

A CLINICAL APPROACH TO SYNCOPE

***Mani Ram Krishna**
****Mohammed Farooq Kunde**

Abstract: *Syncope is a common clinical complaint that a pediatrician encounters in the outpatient clinic or in the emergency room. The causes of syncope include autonomic disturbances, cardiovascular causes and neurological problems. Autonomic syncope is the commonest and is usually benign. Cardiovascular causes can potentially be life threatening and it is important to recognize them and refer these children to an appropriate specialist in a timely fashion. It is possible to identify the cause of syncope in most patients with a detailed history and physical examination. In this chapter, we list the causes of syncope and attempt to provide a clinical approach that will permit accurate triage of patients with syncope by a pediatrician.*

Keywords: *Syncope, Neurocardiogenic syncope, Cardiac arrhythmia, Fainting, Convulsive syncope.*

What is syncope and how common is it?

The word syncope is derived from the Greek work "synkoptein" meaning to cut short. Syncope is defined as an abrupt and transient loss of consciousness associated with loss of postural tone, typically followed by a rapid recovery.[1] The underlying event in all types of syncope is transient cerebral hypoperfusion. Syncope is a common clinical problem in the pediatric age group with most estimates quoting that 15 % of the population would have experienced at least one episode by the age of 18 years.[2] An analysis of pediatric emergency department (ED) visits from the Unites States identified that 0.9% (627,489 of 72,692,311 visits) of ED visits at pediatric teaching hospitals were due to syncope.[3] It is hence clear that syncope is an important clinical problem in the pediatric age group. The vast majority of syncope in this age group can be attributed to autonomic instability, which is usually benign. However, a small but significant group of children (5-10%) may experience symptoms due to a cardiac cause. The differentiation between the two is usually possible by a detailed history and physical examination. In this article, we will present a clinical approach to recognition and treatment of syncope.

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What are the causes of syncope?

The causes of syncope can be broadly classified into three categories (Fig.1): 1) Autonomic Syncope 2) Cardiac Syncope and 3) Others including neurological causes.

Autonomic syncope

Autonomic Syncope accounts for close to 80% of pediatric cases with syncope. Improvement in our understanding of the pathophysiology has allowed us to further categorize this phenomenon into many types.[4]

The commonest and most well understood of these categories is the 'Neuro-cardiogenic syncope (NCS)' also referred to colloquially as "common faint". The typical NCS episode has three components - a prodrome which almost always precedes the loss of consciousness, which in turn is followed by a prompt and usually complete recovery. The pathophysiology of NCS is best explained by the Bezold-Jarisch reflex (Fig.2) - a paradoxical reflex where pooling of blood in the veins results in both a catecholaminergic surge as well as increased vagal tone.[5]

In addition to the 3 components, a careful history will also reveal the presence of precipitants, which tend to decrease the threshold for the event and triggers that bring about the event. The common precipitants in children include hunger, lack of sleep, dehydration, anemia and viral illnesses while typical triggers include sudden change of posture, prolonged upright posture and emotional stress.

The event itself as described earlier is preceded by a typical prodrome of dizziness or light-headedness and nausea. It almost always occurs when the child is standing upright. Syncope in the supine position is one of the pointers towards a non-autonomic cause of syncope and should be investigated further. Most children will be able to recollect the prodrome on questioning. Onlookers frequently mention noticing that the child looked pale just

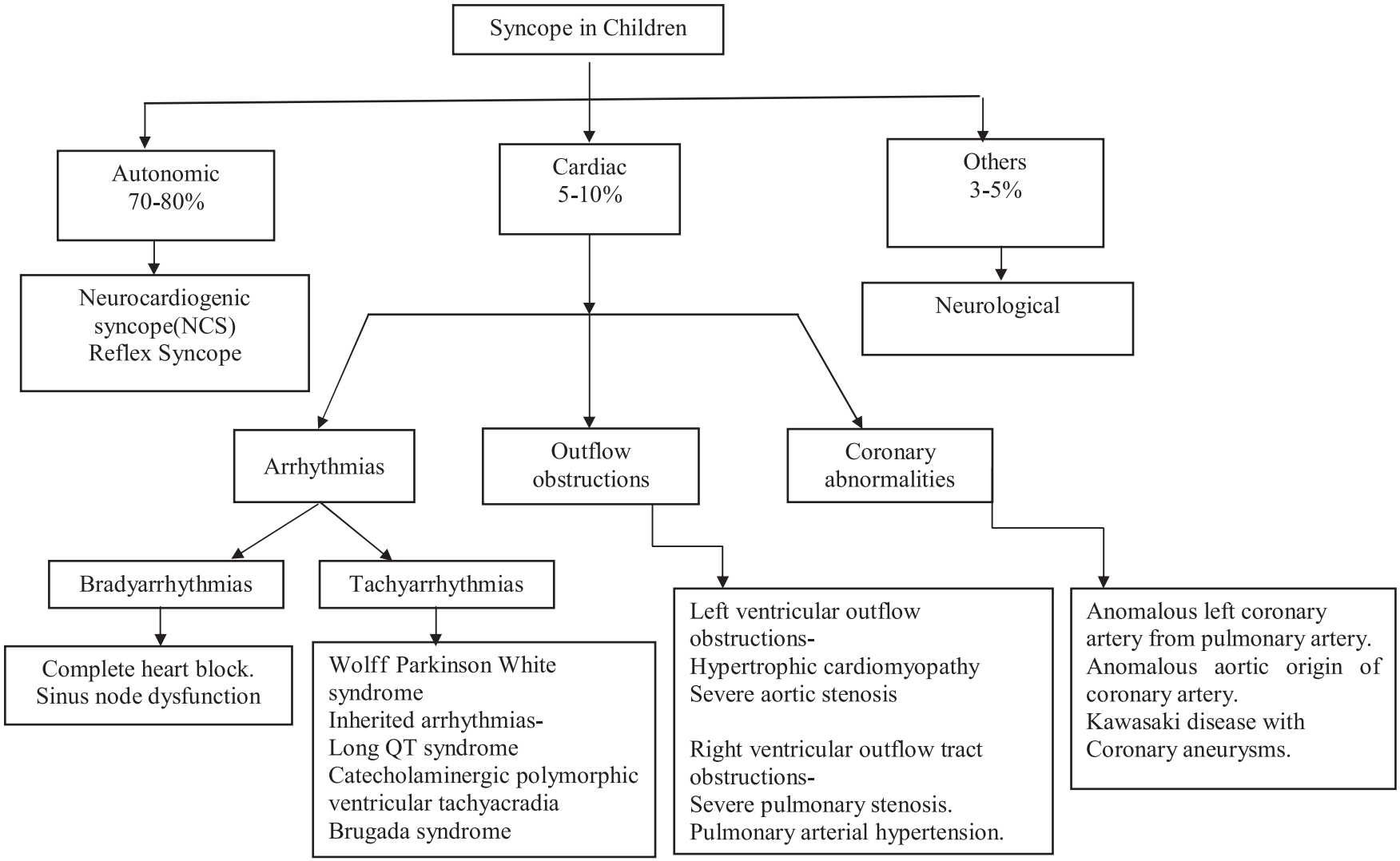

Fig.1. The causes of syncope in children

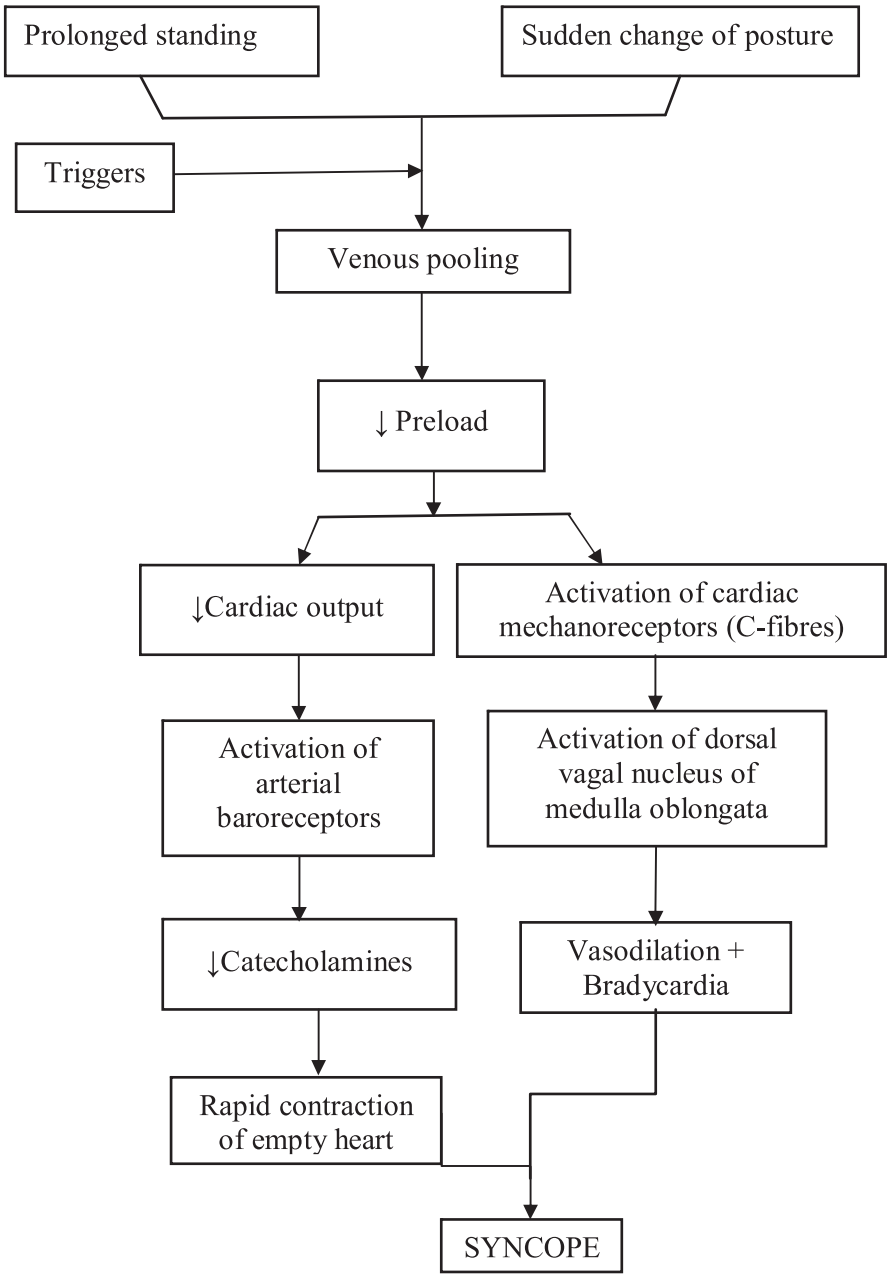

Fig.2. Pathophysiology of Neuro-cardiogenic syncope - The Bezold-Jarish reflex

before the fall. The recovery in NCS is usually instantaneous. There will also be no injury associated with the fall in the majority of cases.

Cardiac syncope

Syncope can be attributed to a cardiovascular cause in approximately 10% of cases.[4] The hallmark of cardiovascular syncope is syncope at the peak of exertion. The cardiovascular causes of syncope can be divided into arrhythmias, outflow tract obstructions and coronary problems.

Outflow tract obstructions (of both the left and right ventricle) are usually fixed mechanical causes. In the resting state, the cardiac output is adequate to match the metabolic demands. However, during exercise, the heart is unable to increase the cardiac output to meet the increased requirements and this results in cerebral hypoperfusion. Frequent co-existing symptoms in this subset include dyspnea on exertion and chest pain.

A peculiar cause of cardiac syncope, which the general pediatrician may not be aware of, is inherited arrhythmias. These are caused by mutations in the genes encoding ion

channels (sodium, potassium and calcium channels). These ion channels control the depolarization and repolarization of cardiac cells and mutations in these channels result in ventricular arrhythmias. The inherited arrhythmias include Long QT syndrome (LQTS), Catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome.[6] The clinical examination after recovery is often normal and the variations in the electrocardiogram (ECG) are often subtle and can be missed by an untrained eye. However, there are very significant clues in the history that raise the suspicion of these disorders. When there is a clinical suspicion, urgent referral to a pediatric cardiologist is indicated to ensure that the diagnosis is not missed.

Syncope due to coronary causes is rare. Kawasaki disease (KD) is fast replacing Rheumatic heart disease (RHD) as the commonest acquired heart disease in children. Children with KD and coronary aneurysm are at a risk for coronary insufficiency during exercise and this can manifest as chest pain or syncope depending on the severity. Anomalous origin of the coronary artery can occur from an unusual location in the aorta (AAOCA) or in rare cases from the pulmonary artery (ALCAPA). ALCAPA more frequently presents in infancy with heart failure. However, in the much rare, adult form of ALCAPA, chest pain and syncope on exertion may be a presenting feature.

Non-cardiac causes

Non-cardiac causes account for less than 10% of syncope. These include neurogenic causes like seizures. It is important to note that cerebral hypoxia may result in convulsive movements even during NCS – a phenomenon referred to loosely as convulsive syncope. A casual bystander may hence confuse this with epilepsy. While clinical differentiation from epilepsy may not always be possible, a few clues can be discerned from a careful history[7]:

1. Prodrome and presyncope – are typical of convulsive syncope and are very unusual in true seizures
2. Tongue biting - is very rare in convulsive syncope and if present is usually at the tip of the tongue unlike the sides during epilepsy
3. Incontinence – typically does not occur in convulsive syncope but is a frequent accompaniment in true seizures
4. Convulsive movement – are usually pleomorphic in convulsive syncope whereas they are rhythmic and uniform in seizures. In recurrent episodes, it may be useful to get one of the bystanders to record a video of the episode
5. Duration - The episode almost always lasts less than a minute in convulsive syncope while true seizures almost always last longer than this. The post-ictal phase is dominated by fatigue in convulsive syncope while confusion is typical of true seizures.

It is important to rule out malingering and other psychogenic causes of seizures especially in adolescents. This is usually difficult to establish clinically. Inconsistencies in the history offer the most important clue towards malingering as the cause of syncope.

Clinical evaluation of syncope

An oft quoted phrase among cardiologists is that "The only difference between syncope and sudden death is that the patient wakes up in one of them". A patient presenting with syncope hence presents a valuable opportunity to ensure that he is not at risk of sudden death. The importance of the clinical assessment in the evaluation of syncope cannot be stressed enough. Indeed, a detailed history is the single most important diagnostic factor in children with syncope.[8]

History

The 5 vital points in history are highlighted in Box 1 and it is imperative that each of these is recorded in detail for each patient. A detailed description of the event may not be available for every episode of syncope. Episodes that occur during school may not always happen under supervision of an adult and peer group children often do not recollect events accurately. In the authors' experience a trigger or precipitant is present in almost every case of NCS and can be obtained by a careful history interspersed with leading questions. Typically, the precipitants include a late-night movie, late night studying before an exam, skipping breakfast and not drinking adequate water in the summer. The triggers include assembly at school and midafternoon sports period.

There are frequently no associated symptoms in children with NCS. However, associated symptoms especially dyspnea on exertion and history of palpitation

Box 1. Key elements in history

- Time of the event
- Activity leading to the event
- Associated symptoms
- Posture at the time of event
- Family history

carry very high specificity for a cardiac cause of syncope. In fact, syncope without prodrome and on exertion along with a history of palpitation has been shown to have a 100% sensitivity and specificity for a cardiac cause of syncope.[9]

The most important finding in history which suggests an inherited arrhythmia is a family history of Sudden Unexpected Death (SUD).[10] The symptoms in inherited arrhythmia disorders include syncope on exertion, syncope triggered by specific stimuli such as shrill sounds or during swimming, syncope while lying supine, family history of sudden unexplained deaths and family history of drowning deaths.[11] Recurrent episodes of syncope during febrile illnesses in a younger child should raise the suspicion of Brugada syndrome. The clinical pointers for a cardiac syncope are summarized in Box 2.

Box 2. The red flag signs which should raise suspicion about a cardiovascular cause of syncope

- Syncope on exertion
- Syncope without prodrome
- Syncope in supine position
- Known cardiac disease
- Known case of Kawasaki disease
- Sudden death in family members (<50years)
- Cardiomyopathy in family members
- Known history suggestive of arrhythmias - Death in other family members due to drowning, syncope after auditory stimulus

Physical Examination

The physical examination in syncope should include the cardiac vital signs i.e heart rate, pulse volume, blood pressure and oxygen saturation (SpO2). When the clinical suspicion is NCS, it is important to look for orthostatic changes in the heart rate and blood pressure. These should be recorded while sitting and after 2-3 minutes of standing. In most cases, these will be normal. However, a tachycardia or hypotension response can prove to be diagnostic. The heart rate is much lower than normal in complete heart block while a low volume, slow rising pulse (pulsus parvus et tardus) suggests significant left ventricular outflow tract obstruction.

The examination of the cardiovascular system should include looking for a parasternal heave (in right ventricular outflow obstruction) as well as cardiomegaly. A harsh ejection murmur at the base of the heart (left or right second inter-costal space) should raise the suspicion of outflow obstruction while a loud pulmonary component of the second heart sound (P2) suggests pulmonary hypertension. The clinical examination is usually normal in children with inherited arrhythmias.

A rapid neurological examination is essential and should focus on possible associations with epilepsy such as neuro-cutaneous markers, signs of raised intra-cranial tension and focal neurological deficits. Finally, it is important to rule out any external injuries that could potentially be related to the fall.

The Electrocardiogram (ECG)

An ECG should be performed in all children in whom a diagnosis of NCS cannot be reliably established at the end of history and physical examination. ECG is a readily available, relatively inexpensive investigation that probably has the highest diagnostic yield in syncope. Typical examples of abnormal ECG have been provided in Fig.3-5. Even if the pediatrician is not comfortable in interpreting the ECG, advancements in technology allows him to obtain the opinion of a pediatric cardiologist from the comfort of his clinic or ED.

In a very small proportion of patients in whom a suspicion of cardiac syncope persists at the end of history, physical examination and ECG, further evaluation by echocardiogram, ambulatory ECG monitoring (Holter) or exercise stress testing will be necessary and this should be done expeditiously by referring them to a pediatric cardiologist. Such tests if performed in those with a negative screen will result in additional economic burden with no diagnostic yield.

Sensitivity of clinical indicators for syncope

The clinical recommendations have been tested in both retrospective and prospective cohorts. Johnson and colleagues analyzed 617 patients who presented with syncope over an18-year period.[11] A screening test of abnormal family history, syncope during exercise, abnormal physical examination and ECG abnormalities had 100% sensitivity for diagnosing cardiac syncope. Tretter and colleagues applied these criteria as an indication for cardiac referral in children presenting with syncope.[12] Approximately 1/3rd of patients with NCS were referred for cardiac evaluation. More importantly, no child with a cardiac syncope was missed.

Practical evaluation of syncope

There is ample scientific evidence that a detailed history, physical examination and an ECG can ensure that

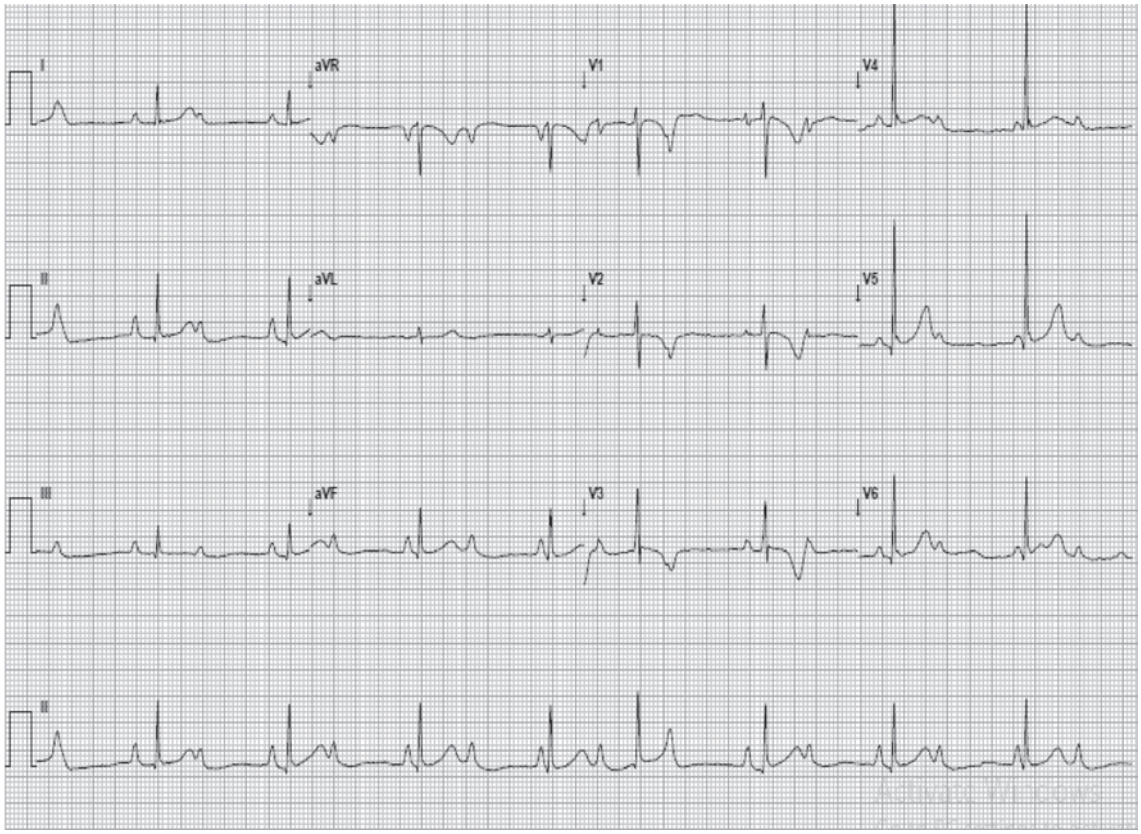

Fig.3. Standardised 12 lead ECG demonstrating bradycardia with no consistent relationship between the p wave and the QRS complex typical of Complete Heart Block (CHB)

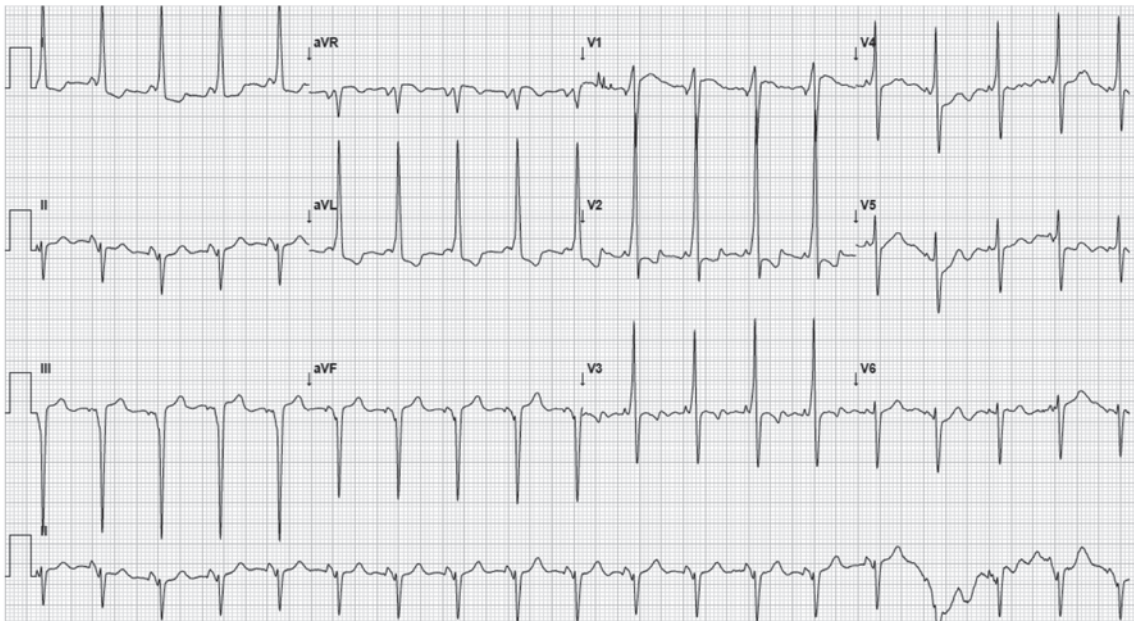

Fig.4. Standardised 12 lead ECG demonstrating sinus rhythm with a short P-R interval, broad QRS complex and a typical slurring of the initial part of the QRS complex (delta wave) in Wolff-Parkinson-White syndrome

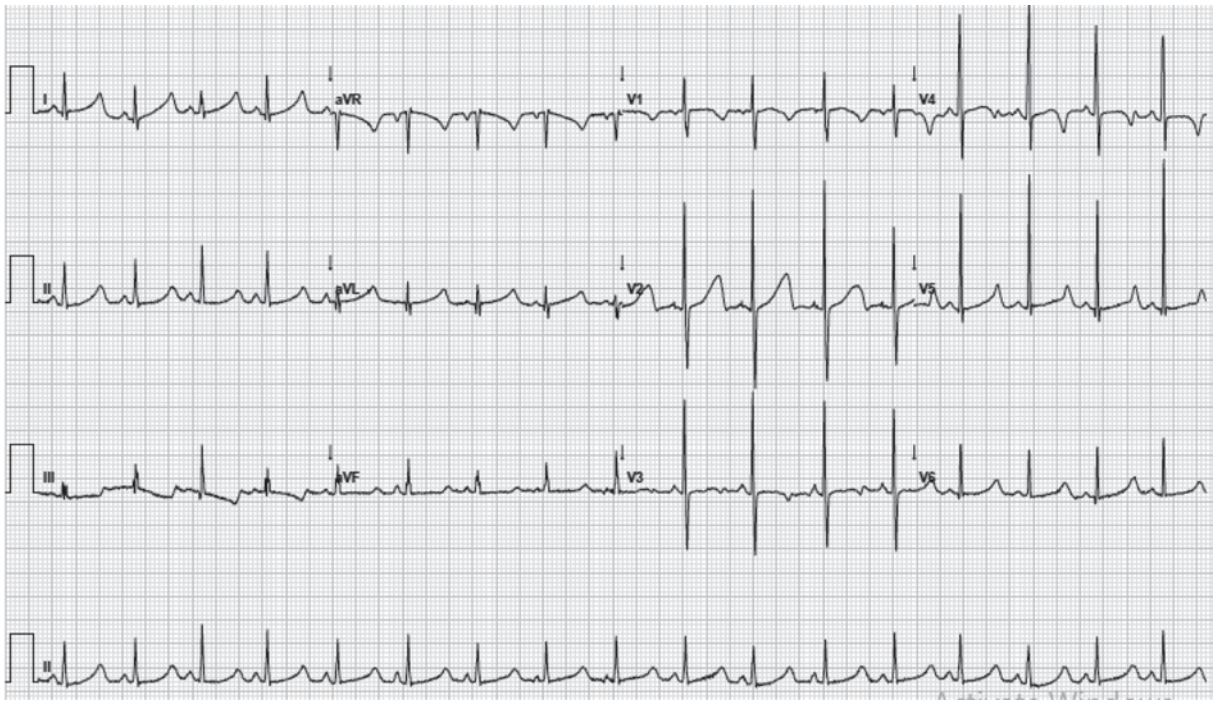

Fig.5. Standardised 12 lead ECG demonstrating sinus rhythm. The T wave is abnormally asymmetrical and the QT interval is prolonged. The QTc in this patient is 540 milliseconds.

no serious cause of syncope will be missed.[8,11,12] This has been made part of recommendations for many years. However, this has not been reflected in clinical practice. Goble and colleagues reviewed workup of syncope in a pediatric ED over a 1-year period.[13] Of the 113 patients who presented with syncope, a minimum of 3 of the 5 key elements of history were recorded in only 60% of patients. Investigations other than ECG were ordered in 89% of patients but a vast majority of tests were non-diagnostic. More than half the patients (58%) underwent a computerized tomogram (CT) of the brain and none of these were diagnostic. Only 10% of patients were admitted but half of these were due to an inappropriate interpretation of the ECG. It is hence clear that the established guidelines are seldom followed in the real world. Unnecessary investigations are frequently ordered. This results in increased anxiety for the patients and also increases the cost of healthcare significantly, an important consideration in resource limited settings in our country. In contrast, the yield of these investigations is virtually nil.

Illustrative case scenarios

Case Scenario 1

A 13-year-old boy was brought to our ED by his physical education teacher on a summer afternoon after he had collapsed at the end of his playtime at school. The boy had played football at school and at the end of the session had gone to drink water with his friends. While awaiting his turn, he had slouched on to the bench behind and fell unconscious. He had recovered within a minute. The boy recollected feeling dizzy but then could only remember waking up surrounded by his teachers. His physical examination was completely normal. His parents arrived half an hour later after being alerted by the school authorities. They confirmed that the boy had no significant past medical history and that there was no family history of SUD. The family had gone to a late-night movie the previous day and the boy had slept for less than 5 hours. A clinical diagnosis of NCS was made. The family was reassured and lifestyle modifications were advised. He was then discharged without further investigations.

Case Scenario 2

A 9-year-old girl was referred to our outpatient clinic from pediatric neurology for evaluation of recurrent syncope. She had been diagnosed as complex partial seizures. However, as the episodes did not improve with treatment, cardiology evaluation was suggested. The parents gave a detailed description of the previous 2 episodes. Once she was carrying a bucket full of clothes up the stairs and collapsed on the top stair. During the other episode, she was dancing along with her sister in front of the television when she collapsed suddenly. Both episodes had clearly occurred at peak exertion. On examination, her vital signs were normal. She however had a grade II para-sternal heave and the pulmonary component of her

second heart sound was very loud, An ECG showed evidence of right ventricular hypertrophy with a strain pattern. An echocardiogram confirmed the diagnosis of severe pulmonary arterial hypertension. There were multiple red flag signs on history and physical examination to merit further evaluation for a cardiac cause of syncope.

Conclusion

Syncope is a common clinical presentation in the pediatric age group. While benign neuro-cardiogenic syncope is the commonest cause, cardiac causes contribute to a small but important subset of these patients. A detailed history and physical examination along with an ECG is adequate to identify all cases of cardiac syncope which require further evaluation.

Points to Remember

- ***Syncope is an important clinical problem in the pediatric age group attending ED.***
- ***There are three groups of causes, autonomic instability which is usually benign and more common, cardiac cause which are serious but less common and others including neurological causes (e.g. convulsive syncope) which are rare.***
- ***The differentiation is usually possible by a detailed history, physical examination and basic investigation like ECG.***
- ***ECG is an inexpensive investigation that probably has the highest diagnostic yield in the evaluation of syncope.***
- ***CT has the lowest diagnostic yield and can be replaced by a good focused neurological examination.***
- ***Unnecessary investigations can be avoided and diagnostic yield can be increased if the pediatrician meticulously takes the history and performs the clinical examination.***

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ADOLESCENCE

ACADEMIC SUCCESS - STUDENT SUPPORT AND GUIDANCE

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Abstract: *Academic success is paramount in any school/ college program. The faculty spent a lot of time to teach many subjects, but often do not guide the students how to study. Poor scholastic performance of school going children is a problem that affect many parents. The predictor variables for poor scholastic performance were; not studying daily lessons, poor concentration in studies, lower education status of father and unhappy family. Early guidance and support may stop students experiencing a cycle of failure. Key to supporting struggling students is to identify reasons for poor performance. Many students lack basic academic skills and do not know how to learn effectively. The transition from school to professional education may affect students emotionally, socially and academically. Recall of information is essential for successful performance in examinations. Better recall can be achieved by time management of study periods and regular systematic learning. Prepare a revision timetable and set out what topics, subjects you want to cover each day.*

Keywords: *Academic success, Scholastic performance, Student support, Enhancing memory.*

Academic success is paramount in any school/college program. The faculty spent a lot of time to teach many subjects, but often do not guide the students how to study. The major reasons for increased attrition rates in school / college education are course failure, stress, burnout, personal health issues, psycho-social problems, financial issues and other family difficulties. Academic failure is a problem for the students, teachers, the school/college and society as a whole. If struggling students could be identified early in the course and additional guidance and support services offered, that will improve the academic skills. Without guidance and feedback, weak students will have ongoing difficulties.

Poor scholastic performance of school going children is a problem faced by many parents. Scholastic backwardness was observed among 10 to 20% high school children. On multivariate analysis the predictor variables for poor scholastic performance were; not studying daily lessons, poor concentration in studies, lower education status of father and unhappy family.[1] A significant number of children with scholastic backwardness in normal schools are slow learners. In a study, children with IQ in the 70-90 range were given individualized education for a period of 4 months and evaluated the effectiveness of an individualized education program (IEP) for slow learners, modeled on resource room training in normal schools. After the training, 87% of children had improvement in either mathematics, reading or writing and 47% had improvement in all the three areas, suggesting that IEP will lead to improvement in academic functioning of children who are slow learners.[2]

Though a small percentage of children with learning difficulties have specific learning disabilities like difficulty with reading, writing and mathematics, the problems in the majority may be attributed to; undetected subnormal intelligence, poor home environment / poor study habits, problems in the school including specific subject problem / poor fit with a teacher and not very uncommonly mental health problems. For example, a CDC-Kerala study on prevalence of depression among adolescents revealed that 11.2% of school dropouts had severe and extreme grades of depression as against 3% among school going adolescents.[3]

Student support and guidance

Early guidance and support may stop students experiencing a cycle of failures. Key to supporting struggling students is to identify reasons for poor performance. Many students lack basic academic skills and

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do not know how to learn effectively. In order to help students overcome their learning difficulties, innovative teaching is required during the first year of higher secondary school/university education, designed to foster the joint development of knowledge, basic skills and right attitude. In the case of less well-prepared students who lack self-confidence, a caring and supportive learning environment is crucial to the achievement of meaningful learning.

Organizing student support and guidance program need specific strategies:

Step.1: Workshops to understand the reasons for course failure,

Step.2: Training support teachers, two from each affiliated school/college,

Step.3: Self-evaluation of study skills,

Step.4: Reaching out directly to the students,

Step.5: Continued support to the students through trained faculty and

Step.6: Establishment of student support and guidance cell in each affiliated school/college by their own faculty and management.

Academic issues and effective learning

The transition from school to professional education may affect students emotionally, socially and academically. The initial exposure to new environment, academic competitiveness, personal independence, large campus, etc can be overwhelming. The students who have entered the university from different academic backgrounds need proper study skills to secure good academic results. Some professional students who perform poorly or drop out during their first year may have common characteristics.

Ten reasons for student's failure[4]

- **Difficulty with medium of instruction**: Sudden shift from mother tongue to English may create problems in understanding and reproducing facts.
- **Lack self-motivation**: Some students lack self-motivation and are unwilling to commit themselves to self-improvement. They are unable to handle ''independence.''
- **Lack of persistence**: Many who fail lack the will to persist because they have little or no career interest. Consequently, they do not have any idea of why they are in college.
- **Negative attitude**: Some students have a negative attitude about themselves, their friends, their class, their college, their neighbourhood, etc. They verbally express this attitude frequently.
- **Wrong priorities**: Some students' priorities do not include educational progress, but do include other activities like, love affair, friendship, etc.
- **Irregular attendance**: Many poor performers do not attend classes or attend infrequently.
- **Uncomfortable with school/college environment**: Some students get lost in the largeness of the institution and do not seek out the many avenues of educational and personal support available to them in the campus.
- **Giving up too quickly**: Poor grades in exam and internal assessment discourage students to regroup and to study.
- **Not being realistic**: Not having a clear idea of what college life is like or how to study effectively. They are overwhelmed with the memorizations and the amount of work required.
- **Practicing procrastination**: Some students do practice procrastination meaning the practice of carrying out less urgent tasks in preference to more urgent ones, or doing more pleasurable things in place of less pleasurable ones, and thus putting off impending tasks to a later time, sometimes to the "last minute" before a deadline.

Strategies to manage procrastination

The first step is to identify why one may be procrastinating and take the following appropriate steps to overcome each one of them;

Fear of failure: To overcome this focus on goal setting, reframe thoughts more positively and simply begin, knowing that one can redraft later.

Anxiety about the task: To overcome this one need to break the task or goal into mini-goals and seek assistance in ensuring that one properly understand the task.

Managing time badly: To overcome this, one has to prioritize tasks and create realistic daily, weekly and term plans.

Have personal issues: In addition to professional support, support from family and friends will be helpful.

Have trouble concentrating: Ensure that the study space is distraction-free and comfortable with good lighting as in a library. Complete the more difficult tasks when one is

most alert. Study when the house is most quiet, perhaps late at night or early in the morning and ask family or friends to support by not disturbing during the study times.

Identifying learning styles and using it positively[5]

At higher secondary / University level a student would be expected to be an independent learner and therefore, it is advisable to think carefully about learning style and how best one can use learning strengths to support academic studies.

Auditory learner: If one is an auditory learner, it means one can learn best by hearing information in the following ways: To read aloud as to learn information; talk through and/or review information with friends; record information on to tape or disc to enable to listen back. Ask a friend to read text or lecture notes aloud; have music playing in the background while one reads or writes and works in a silent room.

Visual learner: Visual learners often learn best from seeing information presented in diagrams, charts or pictures.

Visual techniques: Plan work using spider diagrams, lists or tables, pictograms and mind maps. Write down all information and use colour pens to highlight important information when reading. Use colour paper for different modules or subjects; use large wall charts or planners to organize work; try to visualize information and ideas in mind; change the environment or position in which one works as this may create a link between ones visual settings with a particular subject area.

Kinesthetic learner: A kinesthetic learner will learn best by touching, doing or moving.

Think physically: By discussing ideas with friends; putting different arguments and ideas on separate pieces of paper when planning essays, allows to physically organise answer; going over information in one's mind while walking, jogging or swimming; using colour or draw pictures and diagrams alongside written notes and moving around environment during independent study time.

Multi-sensory learning

It doesn't matter how one learns as long as one uses the methods which suits. However, a combination of the use of all the senses is the best way to learn. Multi-sensory learning can help anyone to enhance the experience of learning and improve recall of important information. Information is received by the brain through the sensory channels. These channels are; visual (seeing information), auditory (hearing information), kinaesthetic (touching, moving or doing), olfactory (smelling and making associations related to smell) and taste (what we experience from the mouth and tongue). Consider how strongly a smell, taste or hearing a piece of music can remind a previous situation or event. This is because all sensory channels work simultaneously to link different emotions to create that experience.

It appears that on average one will remember: 20% of what one reads; 30% one hears; 40% of one sees; 50% of what one says; 60% one does; 90% when one says, hears, sees and does. Multi-sensory learning involves activating as many of the senses as possible at the same time to aid understanding and recall.

Time management for study and leisure

Misuse of time is probably the most common form of mistake that students use to undermine their attempts to study. Defining tasks previously and prioritising activities may help better management of time, even if needs to be altered

Benefits of time management: It is essential for success, allows to spread workload over the course, helps to prioritize workload and to work out how to use time as efficiently as possible, reduces the anxiety and stress that is common whilst meeting the demands of study, decreases the likelihood of tasks being left to the last minute which often compromises performance and helps to schedule time for fun.

The ABC approach: Categorize commitments according to the following groups;

- **A**bsolutely urgent (high importance)
- **B**etter do it soon (medium importance)
- **C**an wait (low importance)

How to manage time effectively: In addition to assessing the ability to concentrate on certain tasks, one needs to learn how to balance personal life with school/ college work. While school/college students devote a significant amount of their time to attending class and studying outside the classroom, they also have personal commitments like work, family and friends they need to take into consideration.

Class notes as a study support system

Making good notes efficiently is a key skill for studying.

General tips for taking notes are as follows

- Notes should contain the date, subject, names of the colleagues, the name of the lecturer and sources of information and page number.
- Different headings for main subject areas on separate sheets of A4 paper as per these notes are liked immediately.
- Put references in the margin, note keywords, indicate if hand-outs on the subject or add information later.
- To leave blank spaces after each note for example. The 'visual image' of notes and blank spaces may help to remember the information recorded. If necessary, use the space to note information you wish to add later.
- Number and/or label notes with headings and subheadings. Indentations and bullet points.
- Highlight to pick key words and phrases. Underline the main points with color pen. Pictures or diagrams may aid their recall.
- To link related notes use arrows, lines, brackets and enclose them in a rectangle.

Preparation and planning for examinations

There are three main forms of examinations, which are commonly used in tertiary assessment. These are multiple choice exams, short answer questions and essay questions. Examinations may comprise combinations of some or all of these alternatives.

Multiple choice questions: Multiple choice questions usually take about a minute each to read, decide on an answer and enter the response. If a question is difficult, mark it, move on and come back at the end if there in time.

Short answer questions: Short answer questions test discreet bits of knowledge and are much more focused than essay questions, therefore responses are expected to be brief and to the point. Usually these types of questions are quite specific, and answers must be specific too.

Essay questions: There will usually be two or three essays to write within the time allowed. In essay questions, the examiner tests understanding of a topic, the concepts and issues, rather than rote memory of facts. Focus and structure are important.

Failure in examinations can be attributed to poor preparation and planning, exam nerves or negative effects of stress. It is important to employ strategies to revise the lessons skillfully in order to ensure better performance in examinations.

Enhancing memory: Recall of information is essential for successful performance in examinations. Better recall can be achieved by time management of study periods and regular systematic learning.

The following techniques will help to improve memory:

- Use multi-sensory methods – Write it, say it, see it, hear it
- Read, recall, review when reading
- Summarize key information onto one page using coloured paper
- Use mind maps
- Put key information into poster format and stick on your wall
- Use colored pens to highlight important facts, to link ideas or to separate arguments
- Record revision notes or answers. Hearing the recorded information may help to remember it
- Group revision may be helpful

Examination related stress, anxiety and depression

Anxiety is the body's natural response to danger, and an automatic alarm when one feel threatened; is under pressure or facing a stressful situation like examination. In order to reduce stress, the students need to make; a realistic revision timetable for model examination and stick to the timetable at any cost; make brief notes of the books, notes and essays to make them easier to digest quickly, especially if one do not like the subject or find it difficult. Most students would benefit by simple tips for reducing stress and anxiety. However, a few may need professional counseling as anxiety disorders and depression are not uncommon in the general adolescent population. In a cross-sectional study involving 201 school going adolescents using Beck Depression Inventory and Screen for Child Anxiety Related Disorders, it was reported that 40.8% showed mild mood disturbance to severe and extreme depression and 54.7% participants had one or the other type of anxiety.[6]

In another cross-sectional study that recruited 537 adolescents aged 11-19 years and 500 out of them completed the study successfully including 36.6% boys and 63.4% girls, the prevalence for all anxiety disorders using the international, Indian SCARED cut-offs and DSM-IV-TR criteria was 8.6%, 25.8% and 14.4% respectively. In the same rural population of adolescents depressive disorders were concurrently present in 23.7% of adolescents with anxiety disorder, while 13.9% had

concurrently only major depressive disorder, 8.3% had only dysthymia and 1.5% had both. Suicidal behavior was increased by the presence of anxiety disorder and being a boy increased the risk of suicidal behavior associated with anxiety disorder.[7]

Academic success - Some simple tips

- Preparing a revision time table incorporating the topics and subjects one should cover each day.
- Best way is to study for a short period and keep some time for relaxation.
- This relaxation time should include walking, cycling, aerobic, exercise, dancing, or swimming anything that de-stress the mind and body.
- Whenever there is difficulty in concentration, it is better to have a break and then to resume studies.
- Highlighting the important and difficult areas will be helpful to make revision as well as to discuss with the teacher and friends for clarity. This discussion will be mutually useful.
- One should not postpone the revision to last hours.
- One should ensure balanced diet; not to miss breakfast which will cause lake of energy, restlessness. This will provide right frame of mind and concentration.
- Ensuring and organizing various needs like pencil, eraser, pens and rulers a day prior to examination is a wise idea.
- Whole question paper should be read with concentration to plan the time for each answer.
- If one question cannot be answered, comfortable question can be attempted first and then the difficult question can be answered later.
- When one gets stressed up, some breathing exercises like deep breathing and slow down breathing may be helpful.

Points to Remember

- ***In addition to teaching individual subjects, every faculty should guide the students on method of study.***
- ***This is implemented by organizing student support and guidance program with specific strategies.***
- ***Faculty should identify reasons for student's failure, and offer specific help.***
- ***Time management by balancing study and leisure time activities.***
- ***Students should be taught about preparing for different type of questions namely multiple choice, short answers and essay.***
- ***Organizing the time, practicing memory enhancing methods, taking balanced diets, controlling the stress, discussing with teachers, combined study and organized revision will help succeed in exam.***

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RADIOLOGY

THE DILATED COLLECTING SYSTEM - 2

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Non-obstructive dilation of the urinary tract

In the previous issue, we saw dilatation of the collecting system due to calculi, pelviureteric or vesicoureteic junction obstruction. Dilatation, however, does not always imply obstruction. It is a common observation when the bladder is overfull. If there is peristent dilatation in post void scan, it indicates obstruction. Bilateral mild hydroureteronephrosis is also seen in polyuric states like diabetes mellitus. Awareness of this can prevent unnecessary investigations.

In Fig.1 there is dilated pelvicalyceal system in intravenous urogram which is often mistaken for a pelvi-ureteric junction obstruction. The calyces are rounded and dilated while the pelvis (PUJ) is triangular and not dilated. This is termed as megacalycosis and if there are more number of calyces, sometimes as many as twenty, it is called polymegacalycosis. Fig.2 is the ultrasound picture

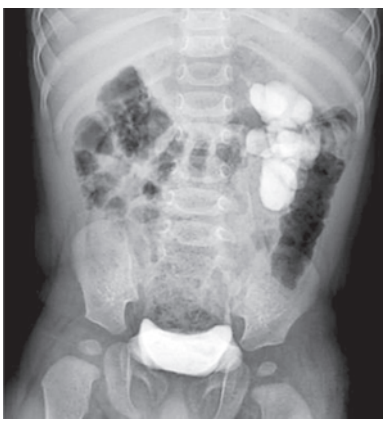

Fig.1. Megacalycosis-IVU

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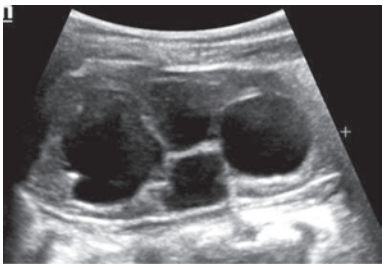

Fig.2. Megacalycosis-USG

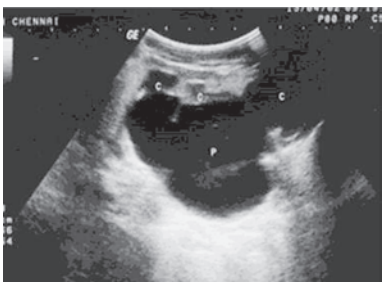

Fig.3. PUJ obstruction

of the same condition, showing a pelvis that is less dilated than the calyces. In other words, the pelvis is not dilated in proportion to the calyceal dilatation. Polymegacalycosis is a dysplasia of the calyces. There is no PUJ obstruction and there is good clearance of the contrast in the later films of intravenous urogram (IVU). The washout pattern in renal scintigraphy is normal. The kidney may be large for age. The cortical tissue around the abnormal calyces is normal in thickness. There is no scarring unless there are bouts of urinary tract infection (UTI) pyelonephritis. The condition is usually diagnosed because of its complications like calculi formation and UTI. Contrast this with PUJ obstruction in Fig.3. The part just proximal to point of block bears the brunt of the obstruction. The pelvis is therefore very much distended.

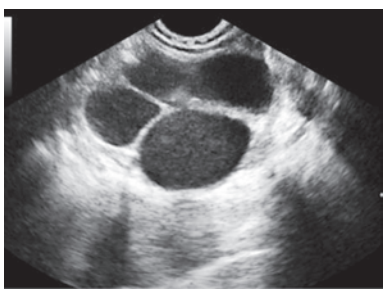

Fig.4.Multicystic dysplastic kidney

Fig.4. shows a kidney consisting of cystic shadows and can easily be mistaken for the pelvicalyceal dilatation in an obstructed kidney. Careful scanning will show that the cysts do not communicate with each other. This is multicystic dysplastic kidney (MCDK). In PUJ obstruction there is a medially placed pelvis communicating with the calyces which are placed laterally, unless there is an associated rotational anomaly. In MCDK, the larger cyst is placed laterally. The MCDK does not carry out excretory function and is known to naturally involute.

It should be remembered that the ureter that is not dilated is not visualised. Ureteric dilatation should always be viewed with suspicion. It is not only signifies obstruction

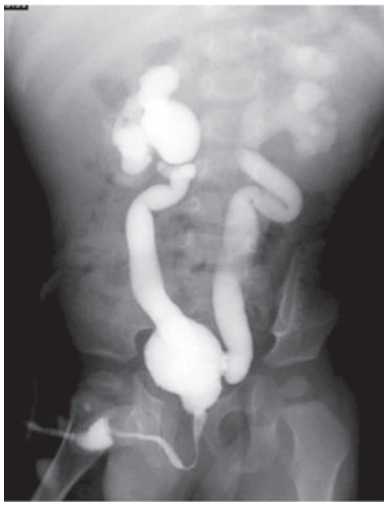

Fig.5. MCU-Grade 5 VUR

but may also be a pointer to vesico-ureteric reflux (VUR). When VUR occurs in a setting of UTI, it may trigger a cascade of events consisting of pyelonephritis, scarring and reflux nephropathy. Therefore all children with UTI are advised ultrasound of the abdomen to look for dilation of the pelvicalyceal system (PCS) or ureter. If present, further evaluation, treatment and follow-up are necessary.

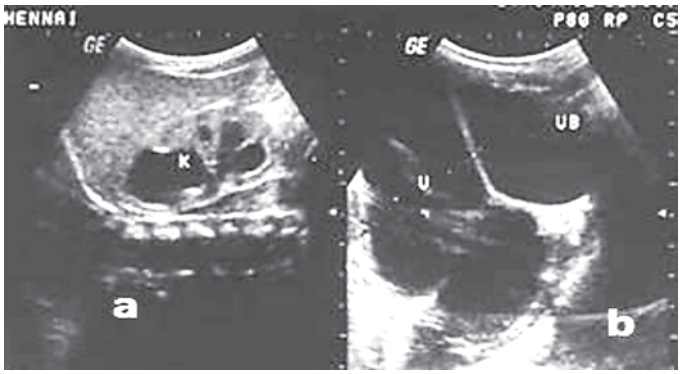

Fig.6a & b.Prune belly syndrome. (UB – bladder and U- ureter)

The gold standard for establishing the presence of reflux is the micturating cysto urethrogram (MCU). This is best done after confirming a sterile urine culture. In this test, contrast and saline are injected into the bladder and films are taken during voiding. The retrograde regurgitation of contrast into the ureter or into the PCS is vesico-ureteric reflux. VUR is graded depending on the level to which reflux is seen and to the state of dilatation of the urinary tract. Grade 1 is reflux of contrast into the lower ureter only. There is no dilation. Grade 2 is reflux of contrast into the pelvicalyceal system and ureter. In grade 3 reflux, the ureter and renal pelvis are mildly dilated. In grade 4 there is blunting of calyces or the calyces lose their normal concavity and the ureter becomes mildly dilated and tortuous. In grade 5 reflux (Fig.5) the ureters are severely dilated and tortuous and the calyces are very much dilated and ballooned out. Therefore the dilatation of the urinary tract in VUR can mimic distal obstruction.

Fig.6a. shows dilated calyces and pelvis and 6b shows grossly dilated and tortuous ureters behind the bladder. The ureteric dilation is grossly out of proportion to the dilated PCS. This appearance is seen in the rare prune-belly syndrome even when there is no obstruction to urine flow.

CLIPPINGS

Pathophysiology of COVID 19 as per current understanding.

While the pathophysiology of this condition is currently unknown, a structural analysis suggests that the virus may be able to bind to the angiotensin-converting enzyme-2 (ACE2) receptor in humans, which suggests that it may have a similar pathogenesis to SARS. However, a unique structural feature of the spike glycoprotein receptor binding domain of SARS-CoV-2 (which is responsible for the entry of the virus into host cells) confers potentially higher binding affinity for ACE2 on host cells compared to SARS-CoV.

Nicholas JB, Tom EF, Robert F. BMJ Best Practice. The BMJ Publishing Group Ltd. web version last updated: Mar 02, 2020. Bestpractice.bmj.com . BMJ Publishing Group Ltd 2020. P6-7.

MEDICOLEGAL MATTERS

PEDIATRICIAN IN DELIVERY ROOM

Cheran B

Prevention is better than cure. A message given tothe patients earlier, is now applicable to doctors too.

Understanding a patient as a consumer gains importance in the present scenario. Times have changed; nine years after the introduction of Consumer Protection Act 1986, from 1995 with VP Shantha's case, doctors were brought into the ambit of Consumer Protection (CP) Act.

Earlier, patients were not winning the cases against doctors and the compensation was very meagre in the few cases they won. Now, in 2020, situations are changing all over India. Doctors lose one in two cases filed against them and awarded compensation which runs to an average of thirty lakhs per case. Hence, doctors have to be very vigilant and cautious.

Recent amendments in CP Act add fuel to fire and following are the few amendments causing great concern to the doctors:

1. Patients can file the cases in their place of residence. If a patient hailing from Assam, got treated at Delhi, he can file the case in Assam itself. Earlier he could file the case only where the hospital was located. This makes it necessary for doctor to travel to far off places to attend the medicolegal cases.
2. Compensation up to one crore can be claimed in the local court where the patient resides. Only when the compensation exceeds one crore, the case has to be transferred to the state capital. For this amount patients need not pay 10% stamp duty.
3. Judges may not always be the presiding officers in Consumer Forums, it can be chaired by social activists and others.

Thus, doctors are at cross roads and have tough times ahead.

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In this issue one such case is analysed. This is a case which had been filed in one of the District Consumer Forums in Tamil Nadu. The treatment had taken place in one of the primary care hospitals in the private sector. The hospital is run by an obstetrician and surgeon together. Among the private healthcare facilities, 30% are taken care of by multispeciality tertiary care hospitals and remaining 70% are managed by the primary care or middle level order hospitals run by small team of doctors.

Brief case details is given below

A pregnant woman was admitted with labour pain around 1.00 am. The doctor on duty administered drug infusion to assist delivery. Though labour pains persisted and the woman was crying in pain, labour did not progress.The obstetrician attended to the patient at 8.00 am, 7 hours after admission to the hospital. Though there were indications for caesarean section, family did not give the consent for caesarean. Obstetrician hurriedly shifted the patient to the operation theatre and delivered the baby by forceps application. There were few lapses here. In the urgency, obstetrician did not brief the family members or obtain proper consent. Pediatrician was not present to attend to the baby during delivery. When the baby got discharged, the prognosis was not discussed and there was no clear follow up advice. Now the child is 7 years old and cannot stand, talk, and is also having recurrent seizures. The child was under the care of pediatrician for the last 7 years. Parents' concern was that no opinion was obtained from neurologist and they were reassured that their child would recover after 5 years. When the parents sought second opinion from another pediatrician, his opinion was different and they got the feeling that there was an element of negligence in the care their child.

Reply from the obstetrician to the court

1. Pregnant woman got admitted for delivery after a delay of one week.
2. Proper intrapartum monitoring was done with electronic foetal monitoring till delivery.
3. There were clear indications for caesarean section, because she was a primi with post dated pregnancy,

mobile head and meconium stained liquor. But her family members were not willing for caesarean and the pregnant mother was also expressing her unwillingness for caesarean to the team of doctors, whenever this option was discussed with her. Hence forceps delivery was done.

4. The baby's head was never lying outside and there were no forceps marks on the head of the baby as claimed by the family members

Order of the court

The following lapses were found on the paediatrician's side.

1. He was not present during this difficult delivery to attend the baby
2. No proper counselling on prognosis and follow up plans were provided to the family, though the pediatrician followed up the child for 7 years.
3. Parents presumed that the child would recover in due course, in the absence of counselling.

Court found the pediatrician to be negligent.

1. Pediatrician should have been present during difficult delivery
2. Parents were not properly counselled about the follow-up and further care of the baby.

Lesson learnt

1. The pediatrician probably wanted to protect the obstetrician and so, he would not have told the parents about the true nature of the problem immediately after delivery . But it is the duty of the paediatrician to discuss on the issues like the status of the neonate, prognosis, and future interventions with the parents at the first consultation itself and record them in the case sheet or in any other document and get it countersigned by them. This document should have been preserved in the hospital records. Another option is a video counselling session. If the circumstances are appropriate, for example if no history of birth asphyxia the pediatrician may say that the insult could have been prenatal and show references from books and explain.

2. General pediatrician should not have managed the case alone for seven long years. He should have referred the patient to a paediatric neurologist or a developmental pediatrician. But in this instance, despite referral they did not go. Unfortunately paediatrician did not have any document to prove that he asked the family to consult a neurologist. As he continued his treatment without cross consultation, parents might have been comfortable with him.

Take home message

- ***Counselling and documentation are vital. Joint counselling with video recording by pediatrician and obstetrician would be a proper option.***
- ***Choosing the correct obstetrician as well the hospital applies not only to the patient, but also to the pediatrician.***
- ***Even though pediatrician had not done anything wrong or was not called earlier prior to delivery, still he would be held accountable, as he had taken the responsibility of taking further care of the child. In order to avoid from the liability, pediatrician has to inform the obstetrician that he should be present during difficult deliveries and not called afterwards.***
- ***Periodical neuro developmental examination by neurologist and developmental paediatrician in the first year will be helpful.***
- ***Discharge summary is a vital document. Discharge advice should discuss about the prognosis and future plan of management.***
- ***These documents have to be preserved along with hospital records.***

CLIPPINGS

Study of lung ultrasonography as a diagnostic tool in childhood pneumonia.

Lung ultrasonography could detect consolidation in more than one lobe than CXR (P = 0.048). Authors have conlcluded that chest ultrasonogram offers an important contribution to the diagnostic procedures of pleuropulmonary disorders in children, such as pneumonia and pleural effusion, with higher sensitivity, specificity, and positive predictive index compared with CXR.

Elmashad GM, Bahbah WA, Mousa WA, Shalaby MM. Study of lung ultrasonography as a diagnostic tool in childhood pneumonia. Menoufia Med J 2019; 32:1043-50.

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