INDIAN JOURNAL OF PRACTICAL PEDIATRICS

- **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**
- **Indexed in Excerpta Medica, CABI Publishing, Scopus**

Vol.18 No.2	**APR.- JUN. 2016**
Dr.P.Ramachandran Editor-in-Chief	**Dr.S.Thangavelu** Executive Editor

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Journal Office and address for communications: Dr. P.Ramachandran, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com

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Published by Dr. P.Ramachandran, Editor-in-Chief, IJPP, on behalf of Indian Academy of Pediatrics, from 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India and printed by Mr. D.Ramanathan, at Alamu Printing Works, 9, Iyyah Street, Royapettah, Chennai-14.

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PEDIATRIC NEUROLOGY

APPROACH TO A CHILD WITH ACUTE FLACCID PARALYSIS

***Naveen Sankhyan**
****Renu Suthar**

Abstract: *Acute flaccid paralysis is a clinical syndrome characterized by rapidly evolving weakness, which may include respiratory and bulbar muscles. Acute flaccid paralysis represents a syndromic diagnosis and can have an array of diagnostic possibilities. This condition can be a medical emergency characterized by rapid progress of clinical signs and symptoms. Immediate management includes supporting airway, breathing, and circulation in these children. Diagnosis is clinical and confirmed by specific investigations. An accurate and early etiological diagnosis has an important bearing on the management and prognosis. This review discusses the approach to a child with acute flaccid paralysis and also discusses some key features of the common causes of acute flaccid paralysis.*

Keywords: *Flaccid weakness, Quadriparesis, Polio, Hypotonic paralysis, Guillain-Barre Syndrome.*

Acute flaccid paralysis (AFP) is a clinical syndrome characterized by rapidly evolving weakness, which may include weakness of the respiratory and bulbar muscles, advancing to maximum severity within several days to weeks.[1] The weakness can be symmetrical or asymmetrical and progresses over days to a few weeks. AFP is a syndromic diagnosis and not an etiological diagnosis. It can be caused by a host of infectious or non-infectious conditions. The term flaccid per se means hypotonia and absence of spasticity or upper motor neuron signs such as hyperreflexia, extensor plantars and clonus. The term 'paralysis' means loss of voluntary muscle contraction due to interruption of neuronal pathways from the cerebral cortex to the muscle fiber. The term 'paresis' is used for mild weakness and 'paralysis' or 'plegia' for severe muscle weakness.[1]

Anatomical localization of AFP is predominantly to spinal cord and the motor unit including anterior horn cells, peripheral motor-sensory nerves, neuromuscular junctions and muscle.[2] Important causes of AFP are acute transverse myelitis (ATM), anterior spinal artery infarct, infectious anterior horn cell myelitis like polio, non-polio enteroviruses, Guillain-Barre Syndrome (GBS), myasthenia gravis and myositis[3] (Table I).

Weakness in children with AFP tends to rapidly evolve and can lead to respiratory and bulbar weakness. Prompt etiological diagnosis of AFP is important for both managementand prognosis. If untreated, AFP can rapidly progress and lead to death due to paralysis of respiratory muscles.

AFP recognition and reporting has immense public health importance and is one of the key strategies in global polio eradication program. For surveillance purpose WHO had defined AFP "as any child under 15 years of age with AFP or any person of any age with paralytic illness if polio is suspected".[4] Polio was the most important cause of acute flaccid paralysis worldwide in the past but with the great success of global polio eradication program, this disease has been eradicated from the Western countries and most of the South East Asian countries. India has been declared polio free in 2014 by WHO.[5] High standards of AFP surveillance have to be maintained in an attempt to identify all cases of AFP. All cases of AFP have to be investigated for evidence of poliomyelitis, for maintaining country's polio-free status. According to the WHO "all AFP cases under 15 years of age or with paralytic illness at an age where polio is suspected should be reported immediately and investigated within 48 hours, and two stool specimens should be collected 24-48 hours apart within 14 days of the onset of paralysis".[4] AFP due to emerging non-polio enteroviruses (Enterovirus 71, Enterovirus D68) has been concurrently reported in the United States, Europe, and China.[6-8]These outbreaks continue to make the recognition of AFP a high priority.[7,8]

In this review the clinical evaluation of a child

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Table I. Etiology of AFP according to the site of involvement at neuroaxis

Site of lesion	Disease
Spinal cord	• Compressive myelopathy Primary extra medullary with extension into the spinal cord: Traumatic myelopathy, vertebral fractures, extradural hematoma, infections like spinal epidural abscess and spinal intra-dural abscess, Pott's spine, discitis, spinal arterio-vascular malformation.
	• Non-compressive myelopathy Inflammatory myelitis:Acute transverse myelitis, neuromyelitis optica spectrum disorders, multiple sclerosis, infectious myelitis (rabies), systemic inflammatory disorders (systemic lupus erythematosus)
Anterior horn cell	• Anterior horn cell myelitis:Polio virus, non-polio enterovirus (coxsackie virus), mycoplasma, Japanese encephalitis,vaccine derived paralytic polio virus, rabies, varicella
	• Vascular: Anterior spinal artery infarct
Peripheral nerves/roots	Immune mediated:Guillain-Barre syndrome - Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) - Acute motor axonal neuropathy (AMAN) CMV polyradiculopathy Porphyria Rabies Critical illness polyneuropathy Toxin-mediated: Post-diphtheritic polyneuropathy, Lyme borreliosis,drug-induced (vincristine), acute porphyria
Neuromuscular junction	Myasthenia gravis, organophosphorus poisoning, snake envenomation, drugs (aminoglycosides), botulism, tick paralysis, hypermagnesemia
Muscle	Inflammatory myositis:Pyomyositis, viral myositis, trichinosis, toxic myopathies, critical care myopathy, periodic paralysis (hypokalemic, hyperkalemic) Dyselectrolytemia: Hypomagnesemia, hypokalemia

presenting with AFP and a practical approach to diagnosis and management are discussed. Localization on the neuroaxis, common etiological possibilities, rational investigation, management of complications and definitive treatment are highlighted.

Clinical approach to a child with AFP

Every child with AFP is a medical emergency requiring rapid assessment, systematic evaluation and immediate stabilization. Initial assessment includes appropriate triage and rapid assessment for airway, breathing and circulation and immediate stabilization. After immediate stabilization, a focused history and examination is advised for localization, etiological investigation and definitive management.

Emergency management issues

1)Respiratory muscle weakness: Careful and serial evaluation includes monitoring for respiratory rate, oxygen saturation, single breath count and chest expansion. Because of profound respiratory muscle or diaphragmatic weakness these children may not show tachypnea or use of accessory muscles but can have significant respiratory acidosis. Respiratory rates can be falsely reassuring in these children. Serial blood gases are required for monitoring. Early elective intubation and respiratory support are critical to save these children (Box 1).

2) Bulbar weakness: Recent onset change in voice, weak cry, pooling of secretions, gurgling sounds in throat, inability to swallow and nasal regurgitation suggest bulbar

Box 1. Clinical parameters useful in assessment of respiratory weakness in children with AFP

- Respiratory rate: Tachypnea, use of accessory muscles
- Swallowing dysfunction and pooling of secretions
- Weak cough
- Reduced speech volume
- Monitoring of single breath count
- Chest rise and abdomen rise
- Tachycardia, diaphoresis

dysfunction. In such situations, the airway is unprotected and is at high risk for aspiration. Elective and planned airway protection is to be done in those children who have bulbar weakness.

3) Toxin and envenomation: Snake envenomation and organophosphorus poisoning are important causes of AFP in children. Every child should be evaluated for a possible toxin exposure. In addition to weakness these children can have profound encephalopathy because of hypoxia. Flaccid paralysis, respiratory weakness, pinpoint pupils and fasciculation suggest an organophosphorus exposure. Sudden onset flaccid paralysis, respiratory weakness, ptosis and external ophthalmoplegia suggest possibility of snake envenomation. Empirical management should be considered if there is a high index of suspicion.

4) Electrolyte abnormalities: Childhood periodic paralysis and hypokalaemia are important causes of flaccid paralysis in children. Assessment of electrolytes and ECG should be sought in all children with AFP.

5) Compressive or traumatic myelopathy: If there is a history of trauma or symptoms and signs suggestive of spinal cord compression (asymmetric weakness, spinal deformity, sensory and bladder dysfunction, fever), an urgent spinal imaging and neurosurgical intervention are needed in these children. Immediate spinal stabilization and steroid administration also is important in these children to prevent long-term morbidity.

History and examination

Younger children with weakness present often with non-specific signs and symptoms such as lethargy, irritability, frequent falls and refusal to stand or walk. An attempt should be made for assessment, quantification and distribution of weakness. Fever at presentation suggests an inflammatory pathology and can be seen in polio, non-polio enteroviral myelitis, transverse myelitis, myositis, epidural, extradural abscess and Potts spine. Symmetrical and ascending weakness suggests diagnosis of Guillain Barre syndrome (GBS), rabies or inflammatory myelitis. Descending weakness suggests diphtheritic polyneuropathy, myasthenia and botulism. Presence of a sensory level, persistent bladder and bowel involvement suggests inflammatory myelitis such as transverse myelitis. Preceding history of upper respiratory infection, acute gastroenteritis can be seen in acute transverse myelitis (ATM), GBS, enteroviral myelitis, polio and polio-like illness. Preceding history of neck swelling and throat pain in an unimmunized child suggests diphtheritic polyneuropathy. It is important to investigate for exposure to drugs, organophosphorus compounds or animal bite and consumption of honey in infants and ingestion of canned food. Fluctuating weakness, diurnal variation, ptosis, bulbar and facial weakness is seen in myasthenia gravis. Unilateral lower limb paresis with a past history of intramuscular injection at gluteal region suggests traumatic sciatic neuropathy. Examination includes assessment for facial, ocular, neck muscle, appendicular truncal weakness, presence of fasciculations, muscle stretch reflexes, plantars, local spinal examination for tenderness, deformity, dermal sinus, para-spinal muscular spasm, bladder and bowel involvement.

Investigations

The following selected investigations are required:

a. Lumbar Puncture: CSF examination is indicated to rule out bacterial or viral CNS infections. Bacterial infections typically show polymorpho-leucocytosis, elevated protein and low CSF glucose. Cultures shows specific organism. CSF should be subjected to multiplex viral PCR to identify the cause of myelitis or flaccid myelitis of viral origin.

b. MRI spine: In selected cases a contrast enhanced MRI spine may be required to rule out spinal cord compression and trauma. MRI shows specific changes for inflammatory myelopathy, demyelinating disorders (ATM), infective myelitis (AFM), spinal cord abscess, anterior spinal artery infarct or neoplasm.

c. Electrophysiology: Nerve conduction studies are required for diagnosis of GBS and its subtypes. Electromyography also helps in diagnosis of anterior horn cell myelitis and myasthenia and botulism.

d. Enzyme studies: Creatine kinase enzymes are elevated in infectious, inflammatory or viral myositis. In suspected organophosphorus intoxication, plasma or red blood cell

acetylcholinesterase activity may be indicated. Anti-acetylcholinesterase antibodies and antibody to muscle-specific kinase (MuSK) help in the diagnosis of myasthenia gravis.

e. Serum electrolytes: The serum levels of potassium and magnesium may be required.

Common causes of acute flaccid paralysis

Guillain-Barre syndrome (GBS)

After polio eradication GBS remains the most common cause of AFP in children. GBS is characterized by rapidly evolving, symmetrical, ascending, flaccid weakness with hypo or areflexia.Weakness progresses in few hours to weeks with maximum severity by 4 weeks. Incidence of GBS in children is about 0.3-1.3 person 100,000 person-year.[9] There are multiple subtypes of GBS; the commonest being acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN).[10] AIDP is the predominant subtype in North America and Europe, while AMAN is more commonly reported subtype in Asia (including India) and Central and South America.[10,11]About 65% of children report preceding upper respiratory tract or gastrointestinal tract infection. Immunopathogenesis involves molecular mimicry and formation of cross-reacting anti-ganglioside antibodies.

Pain, difficulty while walking or refusal to walk are often the first presenting symptoms and subsequently these children tend to develop respiratory weakness, cranial nerve involvement, especially bilateral facial and bulbar muscle weakness (50%), sensory symptoms including painful paresthesia, backache and meningismus (50%-80%). Transient bladder involvement can occur in few children. Approximately 25% develop respiratory insufficiency requiring artificial ventilation and 75% have autonomic dysfunction. The course is monophasic in most children, 80% reach maximum severity within 2 weeks and 97% in 4 weeks. This phase is followed by a relatively static 'plateau phase' ranging from 2 days to 6 months before recovery begins.[9] The diagnosis of GBS is clinical and is supported by a few investigations. Characteristic CSF findings are of albumin-cytological dissociation i,e., a combination of elevated CSF protein and normal cell counts. Nerve conduction studies help in diagnosis of different subtypes of GBS. In the early phase of GBS, motor and sensory nerve conduction study (NCS) can be normal; in such a situation diagnosis is supported by prolonged F-wave latencies. NCS abnormalities tend to peak by 2 weeks of illness. Children with GBS should be managed in PICU during the initial phase. Treatment of GBS involves multidisciplinary supportive care and immunotherapy. Intravenous immunoglobulins and plasma exchange have proven efficacy in treatment of GBS. Indication for immunotherapy includes a Hughes GBS disability scale score ≥3 or when patient is unable to walk unaided for 10 meters (Box 2).[12]

Box 2. Guillain-Barré syndrome disability scale (Modified Hughes GBS disability scale)

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work/capable of running
2. Able to walk without support of a stick (5m across an open space) but incapable of manual work/running
3. Able to walk with a stick, appliance or support (5m across an open space)
4. Confined to bed or chair bound
5. Requiring assisted ventilation (for any part of the day or night)
6. Death

Anterior horn cell myelitis

Onset is with fever, severe myalgia and back pain. Weakness is descending and asymmetric, examination shows meningeal signs, bulbar weakness, hypotonia, normal sensory examination and sparing of bladder and bowel. CSF shows lymphocytic pleocytosis and nerve conduction studies (NCS) suggest anterior horn cell involvement. MRI spine may suggest the diagnosis which may be confirmed by virological studies.

Poliomyelitis: Poliomyelitis is caused by the poliovirus, a neurotropic RNA virus from family picorna viridae, genus enterovirus. The virus has 3 subtypes, poliovirus type 1 is the most frequent cause of epidemic paralytic polio and most neurovirulent subtype. Poliovirus type 2 and 3 are less neurovirulent. Polio infection is transmitted through faeco-oral or oral-oral routes. The incubation period generally ranges from 7-14 days though it can vary from 3-35 days. When un-immunized individuals are exposed to wild poliovirus, 72% develop an inapparent infection, 24% develop a minor illness known as abortive poliomyelitis and 4% patients develop non-paralytic poliomyelitis including aseptic meningitis. Only 0.1%-1% infected individuals develop paralytic disease. The clinical symptoms include fever, headache, vomiting, constipation, neck stiffness, myalgia and acute onset flaccid paralysis during second week of illness. Distinguishing characteristics of paralytic poliomyelitis are onset with a

Table II. Infective etiologies of AFP and their clinical characteristics, diagnosis and management

Cause	Clinical and epidemiological features	Diagnostic investigations
Virus		
Wild polio virus	Febrile onset, asymmetry, myalgia,sensory sparing, CSF-pleocytosis Current transmission in Africa and Pakistan	Viral culture is gold standard but can take 1–3 weeks. Polio PCR on CSF and feces Serology(acute and convalescent titers)
Vaccine derived polio virus	Same as wild polio virus	Same as wild polio
Non-polio enteroviruses	Clinical syndromes similar to wild polio virus; world wide	PCR on CSF, feces, respiratory secretions, blood
Enterovirus 71	Classical hand foot mouth disease with neurological involvement: encephalitis, myoclonic seizures, brain stem encephalitis, acute flaccid paralysis Outbreaks described in Asia-Pacific region.	PCR on CSF, feces, respiratory secretions, blood
Arthropod-borne viruses Japanese encephalitis	Classically presents with encephalitic illness but case series of AFP described Mosquito-borne flavivirus; Asia	PCR on CSF and blood. Serological testing
West Nile virus	Approximately 5%-10% of patients with neuroinvasive disease develop AFP North America, Europe, Africa; isolated case report from India	Serological testing
Dengue	Frequently associated with rash; case reports of AFP described.	NS1 antigen testing on plasma
Rabies	AFP described in rare cases.	PCR testing of skin and saliva Serological testing on CSF and serum
Bacteria		
Diphtheria	Neurological toxicity from absorption and dissemination of diphtheria toxin 3-5 weeks after faucial diphtheria Cranial nerve palsies Motor and sensory impairment	Culture from throat and nose Need confirmation of toxin production
Botulism	Diplopia, ptosis, facial weakness, respiratory weakness, quadriparesis, autonomic features - postural hypotension, Constipation	Isolation of Clostridium botulinum from wound site; Serum assay for botulinum toxin; Electromyography

febrile illness, rapidly progressive paralysis, asymmetric distribution, preserved sensory function, severe myalgia and residual paralysis after 60 days. CSF shows cellular response; proteins are elevated. In children with suspected polio 2 adequate stool samples must be collected and sent for AFP surveillance.[13]

With ongoing efforts for eradication of polio virus many new viral etiological agents are now found to be responsible for polio-like illnesses. Enterovirus 71 has caused epidemics of acute flaccid paralysis in recent years (especially in Asia), often in association with hand, foot and mouth disease.[14] Many other enterovirus, coxsackie

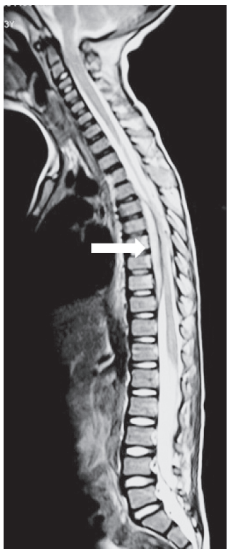

Fig.1. T2W sagittal MRI of the spine showing a fluid collection (white arrow) anterior to the spinal cord resulting in cord compression in a child with epidural abscess.

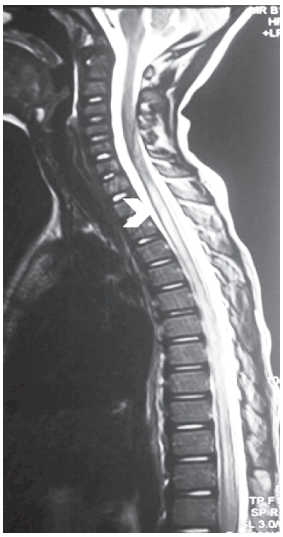

Fig.2. T2W sagittal MRI of the spine showing hyper-intensities (white arrow head) extending over several spinal segments of spinal cord in a child with inflammatory myelitis.

virus and echovirus serotypes and flavivirus occasionally cause cases of AFP.[15] Japanese encephalitis virus typically causes meningoencephalitis, but it can also present with a pure flaccid paralysis.

Acute flaccid myelitis (AFM): Acute flaccid myelitis has been defined as acute onset focal weakness with MRI spine showing predominantly gray matter lesions in the spinal cord. Recently outbreaks of enterovirus D68 associated AFM have been reported from United States.[16] Enterovirus D68 is a picornavirus and causes upper respiratory tract illness in children. Children following an enterovirus-related URTI developed acute flaccid weakness and MRI showed central gray matter involvement. 50% of these patients had specific strain CLAD1 enterovirus D68 in CSF. Neurological involvement in these children was flaccid asymmetric limb weakness, bulbar weakness and cranial nerve dysfunction. Significant proportion of children with AFM had residual motor deficits.[16]

Acute infectious myelopathies: Various infectious agents including viral, bacterial, fungal and parasitic pathogens can cause acute infectious myelitis. Patients are usually febrile, systemically ill and have significant meningismus. CSF shows pleocytosis and elevated protein concentration (Table II).

Acute transverse myelitis (ATM)

ATM is an acute onset symmetric or asymmetric ascending weakness with sensory levels or sensory deficits and bladder and bowel involvement. Respiratory and bulbar involvement can occur with high cervical cord lesion. Examination shows hypotonia, weakness, sensory deficits and persistent bladder dysfunction. Reflexes are absent in acute state and plantars can be mute but later on these patients develop spasticity and hyperreflexia. CSF may show lymphocytic pleocytosis or can be normal. MRI spine is needed for diagnosis (Fig.1,2).

ATM is a group of inflammatory disorders characterized by acute or subacute onset of motor, sensory and autonomic cord dysfunction. The diagnosis of ATM based on transverse myelitis consortium working group (TMCWG) criteria: 1) presence of sensory, motor, or autonomic dysfunction attributable to the spinal cord, 2) bilateral signs or symptoms but not necessarily symmetric, 3) progression to nadir less than 21 days following the onset of symptoms and 4) exclusion of extra-axial compressive pathology by MRI spine.[17] A clearly defined sensory level is difficult to demonstrate in pediatric patients, hence omitted in young children.[18] Clinical presentation includes acute onset flaccid paraparesis or quadriparesis, urinary retention or incontinence, sensory loss or level with absent reflexes and spinal shock. After a few weeks, UMN signs appear, in the form of spasticity and hyperreflexia. Compressive pathologies and other causes of acute myelopathy like trauma, anterior spinal artery infarct, epidural abscess, and hematoma need exclusion in this setting. ATM can be a monophasic illness or part of relapsing-remitting demyelinating disorders. About 75% children with ATM

have longitudinal extensive myelitis (LETM >3 spinal segments).[18] Serum anti-aquaporin 4 antibodies should be done in all children with LETM for diagnosing neuromyelitis optica spectrum disorders. Evaluation of optic nerve involvement with visual acuity assessment and screening MRI brain is warranted in these children. The management consists of immunosuppression and supportive care. Methylprednisolone is given in a dose of 10-30 mg/kg/d (max:1 g/d) for 5 days followed by oral prednisolone 1-2 mg/kg/day for 2 weeks and then tapered over subsequent 2-4 weeks. Outcome is guarded as about 40%-50% children tend to have persistent motor and bladder dysfunction.[18]

Traumatic neuritis

Traumatic neuritis is suspected in cases where there is acute onset monoparesis occurring in temporal correlation with IM injection in that limb. It is associated with pain and hypothermia of the affected limb. Sciatic neuropathy due to intramuscular injection in the gluteal region is the commonest form of traumatic neuritis in the developing world. It is sometimes difficult to distinguish from polio. However, sensory deficits and lack of CSF pleocytosis favor the diagnosis of traumatic neuritis. Management is entirely supportive.

Diphtheritic polyneuropathy (DP)

Diphtheria is caused by toxigenic strains of Corynebacterium diphtheria. First symptoms include presence of low-grade fever, sore throat, neck swelling, palatal palsy and nasal twang. DP typically occurs 3-5 weeks after the onset of diphtheria. About 20% of patients with diphtheria develop DP. The main clinical features include sensory and motor signs and symptoms, descending paralysis with reduced or absent deep tendon reflexes. Severe weakness with quadriparesis and respiratory weakness can occur in one third children with DP and all have sensory and autonomic dysfunction.[19] NCS shows predominantly demyelinating polyneuropathy. Management is in the form of aggressive and supportive care. Diphtheritic polyneuropathy though disabling is generally not fatal and resolves with time. Mortality in diphtheria is due to myocarditis, cardiac arrhythmia, respiratory paralysis and laryngeal weakness.

Hypokalemic paralysis

This is an important differential in any child particularly in a younger child with AFP. An early recognition can prevent potentially fatal cardiac complications. In the developing countries,it most commonly results from diarrheal diseases. Other conditions like celiac disease, renal tubular acidosis, familial periodic paralysis and primary/secondary hyperaldosteronism also need to be considered. Correction of potassium levels rapidly reverses the paralysis in these children.

Points to Remember

- ***Acute flaccid paralysis in children is a medical emergency.***
- ***AFP is a clinical syndrome with array of differential diagnosis.***
- ***The common causes of AFP are Guillain-Barre syndrome, anterior horn cell myelitis and acute transverse myelitis.***
- ***Rapid evolution of the weakness can lead to respiratory failure. Hence a child with AFP should be managed in PICU in the initial few days.***
- ***AFP surveillance is a key strategy for global polio eradication.***

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PEDIATRIC NEUROLOGY

APPROACH TO A CHILD WITH ATAXIA

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Abstract: *Ataxia is a relatively common neurological problem in children which encompasses a wide range of causes from infections to inherited disorders. The history and clinical examination coupled with appropriate investigations including neuroimaging can lead to an appropriate diagnosis. Some of these diseases are treatable while the other inherited ataxias require genetic counseling for the patients and their families.*

Keywords: *Ataxia, Cerebellar, Childhood*

Ataxia is a broad term that refers to disturbance in the smooth performance of voluntary motor acts.[1] It is an inability to coordinate voluntary muscle movements that cannot be attributed to weakness or involuntary muscle activity. The term ataxia is derived from the Greek word 'ataktos' meaning lack of order.[2] Ataxia in children can be due to disorders affecting the cerebellum, vestibular system or proprioceptive sensory system. Often it is observed in lesions of the cerebellum or its connections (afferent or efferent) or both. The cerebellum was recognized as a distinct division of brain by Greek physician Herophilus. The first extensive clinical studies on cerebellum were done by Holmes who studied the sequelae of gunshot wounds in World War I soldiers. He was the one who first defined the clinical features of cerebellar syndromes.[3]

Anatomy of cerebellum

Cerebellum follows the rule of three - has 3 lobes, 3 layers, 3 nuclei and 3 peduncles (Box.1 and Fig.1).

Box 1. Cerebellum – characteristics

Anatomy	- Anterior lobe, posterior lobe and flocculo nodular lobe.
Phylogeny	- Archicerebellum, paleocerebellum and the neocerebellum.
Layers	- Cortex, white matter and deep nuclei from exterior to interior.
Nuclei	- Fastigial nuclei, interposed nuclei (nucleus globose and emboliformis), dentate nuclei.
Peduncles	- Superior cerebellar peduncle which connects it to midbrain, middle cerebellar peduncle to pons and inferior cerebellar peduncle to medulla

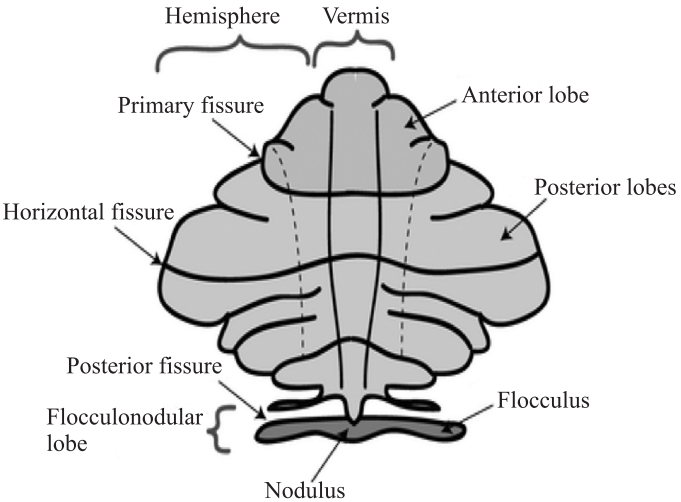

Fig.1. Anatomy of cerebellum

Functions of cerebellum

The cerebellum integrates multiple sources of sensory information and utilizes this information to coordinate motor movements.[1] The main functions are to coordinate voluntary movements, maintain equilibrium and muscle tone. It organizes the range, velocity, direction and force of muscular contractions to produce steady volitional movements and maintains posture. The cerebellum also participates in learning motor tasks, because its function can be modified by experience. The functions of the different regions of cerebellum are given in Table I.

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Table I. Connections and functions of cerebellum

Division	Function
Flocculonodular lobe (Archicerebellum)	Maintenance of equilibrium, control of reflexive head and eye movements
Vermis (Paleo cerebellum/Spinocerebellum)	Regulation of limb movement and posture (Axial and proximal muscle control)
Intermediate zone (Paleo cerebellum/Spinocerebellum)	Regulation of limb movement and posture (Distal muscle control)
Lateral zone (Neocerebellum/Cerebrocerebellum)	Motor planning, initiation and timing

Cerebellar dysfunction: The classical signs of cerebellar dysfunction are described in Box 2. Damage to the cerebellum disrupts coordination of limb and eye movements, impairs balance and decreases muscle tone.

Distinguishing features of cerebellar ataxia from vestibular and sensory ataxia

Balance and coordination problems in children can be due to disorders affecting cerebellum, vestibular system and / or peripheral sensory nerves.[4] Vestibular ataxia is characterized by prominent vertigo. It spares the limbs and speech. The typical feature of sensory ataxia is worsening of ataxia during darkness and when visual cues are blocked (eyes closed - positive Romberg's sign) associated with decreased joint, position and vibration sense. There is no vertigo or dizziness and speech is spared.

Cerebellar ataxia - etiology[5,6]

Cerebellar ataxia in children can be discussed as whether (1) inherited or acquired (2) acute, recurrent or chronic and (3) static or progressive if chronic.

Inherited cerebellar ataxias are an extremely heterogenous group of disorders. The mode of inheritance in inherited ataxias is mostly autosomal recessive. Autosomal dominant (typically adult onset, although some varieties have a childhood onset), X-linked and maternally inherited forms (mitochondrial) are other modes of inheritance. Acquired causes include drugs/toxins, immune mediated/demyelinating, vascular, brain injury, neoplastic/ paraneoplastic disorders.

Acute ataxias

Acute ataxia refers to a symptom evaluation time of less than 72 hours.[7]

The various causes of acute ataxia and their characteristic features are depicted in Table II.

Box 2. Clinical signs of cerebellar disease

Titubation: Bobbing or swaying of head and trunk in a sitting position.

Nystagmus: Horizontal, gaze evoked, with slow phase followed by rapid saccadic correction.

Dysarthria: Unclear pronunciation with normal language content and meaning; scanning speech – abnormally long pauses between words or syllables

Hypotonia: Decreased muscle tone

Dysmetria: Errors in judging distance, tested by finger-nose test, which may result in underestimation (hypometria) or overestimation (hypermetria)

Past pointing: Termination of a movement, briefly, away from the target, tested by extending the arm in front, raising it, and attempting to return it to the identical position.

Intention tremor: Tremor occurring at the end of the movement when attempting to make a directed movement such as approaching a target

Dysdiadochokinesis: Impaired rapid alternating movements, tested by alternating supination and pronation of hands.

Impaired check (Rebound phenomenon): Failure to arrest a limb movement, tested by flexing the arm at the elbow against resistance that is suddenly released.

Truncal ataxia: Oscillations while sitting or standing; falling may occur toward the side of a unilateral lesion.

Wide-based gait: Feet placed widely apart, broad based gait; difficulty standing with feet together or defective tandem walking.

Table II. Causes of acute ataxia in children

Cause	Epidemiology	Diagnostic features	Tests
Infectious and post-infectious - varicella, coxsackie B, EBV, influenza A and B, entero / echo viruses, mycoplasma, legionella.	Accounts for 40% of all ataxias in children. H/O antecedent illness 1-3 weeks earlier in 70% of the cases. Most common in children of 2-4 years age	Significant gait and truncal ataxia, extremities are less affected, sensorium remains clear throughout the illness, maximum findings at onset, improving over few days, self-limiting and benign course, recovery usually in less than 2 weeks.	CSF - Mild pleocytosis, negative bacterial and viral cultures. MRI brain - Usually normal, may show mild, non-specific changes.
ADEM	H/O viral infection or vaccination 2-3 weeks earlier Mean age 6-8 years	Associated with altered sensorium, seizures and multi focal neurologic deficits. Systemic symptoms such as fever, headache, meningism are common. High dose steroids is the treatment Recovery over 4-6 weeks	MRI brain - Multifocal, patchy subcortical white matter demyelination in cerebral and cerebellar hemispheres, basal ganglia, brain stem and spinal cord. CSF - Pleocytosis, increased protein
Drugs Anticonvulsants- phenytoin, carbamazepine - at therapeutic serum levels; benzodiazepines, barbiturates - at higher serum levels; phenothiazines, antihistamines	Accounts for 1/3 rd of all acute ataxias Bimodal age distribution : < 6 years - Accidental, adolescents - Substance abuse	Ataxia is often accompanied by nystagmus, lethargy, confusion, inappropriate speech or behaviour A high index of suspicion is necessary[8]	Serum toxin screen
Miller Fisher variant of GBS	H/O viral infection, diarrhea or vaccination 2-3 weeks prior to the onset of the illness	Ataxia, ophthalmoplegia and areflexia IV immunoglobulin or plasmapheresis is indicated.	CSF- cyto albumino dissociation Serum GQ1b antibody positivity
Vascular	Uncommon in children	Vascular occlusions, malformations from vertebral or basilar arteries, cerebellar hematomas can cause ataxia.	MRI brain with MRA gives the diagnosis Further workup depends on infarct or bleed

Cause	Epidemiology	Diagnostic features	Tests
Opsoclonus Myoclonus Ataxia syndrome	Immune mediated paraneoplastic phenomenon to neurobalstoma or post viral Usually in toddlers and preschool children, 65% of children with OMA have occult neuroblastoma Neurologic symptoms can precede the tumour by months or even 2 years in some cases.	Irritability, rapid, chaotic, multidirectional ocular movements (opsoclonus/ dancing eyes), gait and truncal ataxia with notable tremor of entire body, multifocal myoclonus ACTH, immunotherapy are useful Surgical removal of neuroblastoma, chemotherapy	USG/CT chest, abdomen will show the tumour in the posterior mediastinum or adrenals. Since the tumours are usually low grade, urine for VMA, metanephrines is helpful only if results are positive. Total body MIBG nuclear scan or Gadolinium enhanced MRI of pelvis, abdomen, chest and neck to find out occult neuroblastoma

Episodic or intermittent ataxia

The causes include hereditary episodic ataxias and metabolic disorders presenting as intermittent ataxia (Table III). Autosomal dominant inherited episodic ataxias are channelopathies and may respond to acetazolamide or phenytoin. Otherwise intermittent ataxias should particularly raise the suspicion of underlying inborn error of metabolism. Acute exacerbation usually follows high protein ingestion, inter current infection or physical stress. Intermittent ataxia may or may not be associated with lethargy and vomiting in such cases. Occasionally migraine and benign positional vertigo of childhood can present as intermittent ataxia.

Chronic static ataxias (Congenital ataxias)

Congenital ataxias are frequently genetic and they include cerebellar/vermian agenesis and hypoplasia, more complex cerebellar dysgenesis (Joubert syndrome and associated disorders, Gillespie syndrome, rhombencephalosynopsis), may have contributory environmental causes (Chiari malformations, Dandy Walker and its variants). The clinical features and neuro imaging features are described in (Table IV).

Although congenital ataxias are static and non-progressive, it may be difficult to distinguish them from children with early-onset progressive ataxia and cerebellar atrophy. In such circumstances, historical information is extremely valuable, as congenital patients frequently come to attention around the time of ambulation, but symptoms may have been present earlier. Conversely, congenital ataxia with subtle features can often be overlooked, particularly by parents who may interpret mild gait or hand ataxia as normal in a toddler.[7] Descriptions of play activity, feeding behavior, etc. may help identify clues to the initial appearance of ataxia findings.

In infancy, the presentation is delayed motor and language milestones, and hypotonia. As a toddler, the situation is dominated by impaired motor performance, avoidance of difficult tasks. Ataxia becomes more evident on gait initiation and changing gait direction. With age, impaired coordination, delay in cognition and language become more obvious. As the child grows, ataxia improves and the main concerns are intellectual impairment and seizures.

Some gene loci/genes (e.g. VLDLR, CA8, ZNF592, WDR81) have been identified in isolated congenital ataxias and non-progressive cerebellar 'ataxia plus' syndromes (deafness, optic atrophy, short stature).

Additional acquired causes of congenital ataxia can include secondary damage from neonatal hypoxic-ischemic encephalopathy or intrauterine strokes.[11]

Table III. Causes of intermittent ataxia in childhood

Disorder	Distinguishing clinical features	Treatment
Episodic ataxia type 1-7	Autosomal dominant inheritance, positive family history, patient normal in between the attacks. Physical exertion and emotional stress are the triggers. Episodic ataxias 1,2,7 have childhood onset. EA 1 - mutation in KCNA1 gene EA 2- mutation in CACNA 1 gene, most common[2] EA 7- seizures, attacks of vertigo, slurred speech[9]	Acetazolamide
Maple syrup urine disease intermittent form	Lethargy, vomiting, branched chain aminoaciduria during episodes of fever, infection	Protein restriction, riboflavin
Mevalonate kinase deficiency	Hypotonia, mental retardation, retinal dystrophy, mevalonic aciduria[10]	Protein restriction
Biotinidase deficiency	Alopecia, dermatitis, seizures, developmental delay	Biotin
Urea cycle defects	Lethargy, vomiting during episodes of fever, infection, hyperammonemia, alkalosis	Protein restriction, sodium benzoate, arginine
Pyruvate dehydrogenase deficiency	Hypotonia, mental subnormality, microcephaly, failure to thrive, lactic acidosis	Ketogenic diet
Mitochondrial complex defects I, III, IV	Psychomotor delay, pyramidal signs, respiratory defects, recurrent vomiting, dystonia	Riboflavin, Co Q
Refsum disease	Icthyosis, retinitis pigmentosa, cardiomyopathy, peripheral neuropathy, defect in phytanic acid metabolism	Dietary restriction of phytanic acid

Chronic progressive ataxias

Brain tumours are an important cause of progressive cerebellar ataxia. Around 50% of all brain tumours arise from the brainstem or cerebellum. Posterior fossa tumours usually present with slowly progressive ataxia and symptoms of increased intracranial pressure.

Genetic, inherited metabolic and degenerative ataxias

Autosomal recessive ataxias are the most common class of genetic ataxia seen in children, with typical onset before the age of 20 years.[12] Incidence is approximately 4 cases per 100000 persons worldwide. The presence of multiple affected siblings and/or consanguinity can suggest this form of inheritance.

Clinically, autosomal recessive genetic ataxias typically develop as slowly progressive and symmetrical gait and limb ataxia, often associated with sensory or sensorimotor polyneuropathy. Involvement of other organ systems outside the central nervous system can often be seen as well, and can be useful diagnostically. Unfortunately, for the majority of genetic ataxias, including the most common, established treatments are still lacking. However in some of these diseases, treatments are available to arrest or slow the disease course if identified and treated early.[4] It is therefore important for the physician to recognize these cases to begin therapy and screening must follow or be coupled with an evaluation for acquired causes to ensure that treatable etiologies have been excluded.

An important consideration at this juncture is proper counseling of the parents and families about the illness, possible treatment, prognosis for the proband, mode of genetic transmission and the prospective risk of

Table IV. Causes of congenital ataxia

Disease	Cause	Clinical features	Neuro imaging & others
Joubert syndrome and related disorders (JSRD)	Mutation of primary ciliary protein genes	Episodic hyperpnoea, oculomotor apraxia, nystagmus, encephalocoele, retinal dystrophy, renal cyst, polydactyly, facial dysmorphism	Molar tooth sign, key hole or triangular IV ventricle
Gillespie syndrome	Mutation in PAX6 gene	Aniridia, dysmorphism, hypotonia, mental retardation	Vermian hypoplasia, cerebral atrophy
Congenital disorders of glycosylation (CDG)	PMM2 gene in CDG 1a (commonest CDG)	Seizures, pigmentary retinopathy, coagulopathy, inverted nipples, subcutaneous fat pads, liver fibrosis, cardiomyopathy,	Cerebellar hypoplasia, isoelectric focusing of serum transferrin
Rhombencephalosynopsis	Lack of induction of vermis	Facial dysmorphism, squint, nystagmus, failure to thrive, poor suck and swallow, head rocking, seizures	Absent vermis, fusion of cerebellar hemispheres
Chiari malformation	Unknown probable factors include genetic factors, exposure to chemicals, alcohol consumption, lack of vitamins and nutrients during pregnancy	Dizziness, headache, neck pain (worsened by coughing), lower cranial nerve palsies (swallowing and feeding difficulties, stridor, apnoea, weak cry, down beat nystagmus)	I- Herniation of cerebellar tonsils II- Herniation of lower brainstem with myelomeningocoele III- With occipital encephalocoele IV - cerebellar agenesis
Dandy walker malformation	Exposure to toxins viral infections during pregnancy, maternal diabetes, chromosomal defects	Large head, irritability, vomiting, excessive sleepiness, nystagmus	Agenesis of vermis, cystic dilatation of IV ventricle, enlarged posterior fossa

recurrence.[10] To provide an accurate advice in this rapidly expanding field, familiarity with current literature and consultation with a clinical geneticist is necessary. The causes for inherited chronic progressive ataxias with their characteristic feature are depicted in (Table V).

Approach to a child with ataxia

Since there is a diverse group of conditions that can cause ataxia in children, a systematic approach is essential. The first step would be to distinguish between cerebellar ataxia from vestibular causes and posterior column dysfunction. Next is to go by the tempo of the illness - whether the onset is acute, subacute, chronic and whether the illness is static, improving or progressing. A detailed clinical history will often give a clue to the cause of ataxia. History of trauma, infection, headache, vomiting, drug ingestion, recent exanthem, vaccinations may suggest important considerations. The age of onset of ataxia and family history are important in elucidation of possible diagnosis in inherited ataxias (Table VI). A thorough physical examination often provides vital clues to the diagnosis (Table VII & VIII), though physical examination may be difficult as ataxic children are often uncooperative and irritable.[17]

A thorough neurological examination including the cerebellar signs, involvement of higher functions,

Table V. Causes of inherited ataxia

Disease	Gene (protein defect)	Characteristic features apart from cerebellar signs	Neuro imaging & other investigations	Treatment
Friedreich ataxia (FRDA)	FXN (Frataxin Trinucleotide repeat disorder GAA repeats 66 - >1700 Normal 7-38	Most common inherited ataxia Prevalence 2-4.5/100000 Hypoactive knee and ankle reflexes, extensor plantar, impaired position and vibration sense, optic atrophy, sensorineural hearing loss, hypertrophic cardiomyopathy, skeletal abnormalities(kyphoscoliosis, pes cavus), diabetes	Thinning of cervical spinal cord, abnormal signals in dorsal and lateral columns Abnormal ECG, ECHO NCS - Axonal neuropathy DNA mutation analysis	CoQ, antioxidants (mitoquinone, idebenone)
Ataxia telangiectasia (AT)	ATM (Ataxia telangiectasia mutated)	Telangiectasia (bulbar conjunctiva, pinna, soft palate), oculomotor apraxia, recurrent sinopulmonary infections, choreoathetosis, mental subnormality, immune deficiency, increased incidence of lymphoreticular malignancies, chromosomal instability	Cerebellar atrophy Reduced IgA, IgE, IgG2 Serum α feto protein >10ng/ml High Carcino Embryonic Antigen	Amantadine, fluoxetine may help the loss of balance and impaired speech. Tremors can be controlled by clonazepam, propanolol or gabapentine[13]
Ataxia telangiectasia like disorder (ATLD)	MRE 11A (Meiotic recombination-11protein Defective DNA repair)	Oculomotor apraxia		
Abeta lipoproteinemia (ABL) (Bassen - Kornzweig syndrome)	MTTP (Microsomal triglyceride transfer protein Virtual absence of apo lipoprotein B and apo	Malabsorption(steatorrhoea, abdominal distension), hyporeflexia, Babinski , peripheral neuropathy, cardiomegaly, arrhythmias,retinitis pigmentosa, pes cavus,	Cerebellar atrophy PS - Acanthocytes low LDL, VLDL,	Vitamin E Other fat soluble vitaimins - A,D,K

	lipoprotein B containing lipoproteins in plasma)	scoliosis	triglycerides low levels of vitamin A,D,E,K DNA mutation analysis	
Ataxia with vitamin E deficiency (AVED)	TTPA (Alpha tocopherol transfer protein)	Similar to Friedreich ataxia, hyporeflexia, Babinski, peripheral neuropathy, head titubation, pigmentary retinopathy, foot deformity Skin xanthalasma, tendon xanthoma In contrast to Friedrich, cardiomyopathy and glucose intolerance are less frequent	Absent to low fasting vitaminE Vitamin E <2.5mg/L[12] High cholestrol, triglycerides	Vitamin E lifelong - 40mg/kg/day
Refsum disease (RD)	PHYH (Phytanoyl coA hydroxylase Defect in α oxidation of phytanic acid)	Night blindness, cataract, pigmentary retinopathy, peripheral neuropathy, deafness, icthyosis, cardiac arrhythmia	High phytanic acid in blood and urine	Dietary restriction of phytanic acid, plasma exchange
Autosomal recessive ataxia of Charlevoix-Saguenay (ARSACS)	SACS (Sacsin)	Spasticity, peripheral neuropathy, retinal striations, thickened retinal nerve fibre layer	Vermian cerebellar atrophy, thinning of cervical spinal cord, linear hypointensities in pons Mutation studies	Physiotherapy, antispasticity drugs
Ataxia with oculomotor apraxia (AOA1)	APTX (Aprataxin)	Identical to AT without non-neurological features[14] Oculomotor apraxia, dystonia, choreoathetosis, optic atrophy, peripheral neuropathy, intellectual disability	Cerebellar atrophy Hypoalbumine mia	
Ataxia with	SETX	Oculomotor apraxia, axonal	Cerebellar	

oculomotor apraxia (AOA2)	(Senataxin)	neuropathy, dystonia, choreoathetosis, normal intelligence[15]	atrophy High α feto protein levels	
Cerebrotendino xanthomatosis (CTX)	CYP27A1 (sterol 27-hydroxylase)	Tendon xanthomas in Achilles tendon bilaterally, cognitive decline, dystonia, cataract	Cerebral white matter changes, cerebral and cerebellar atrophy[16] Normal or low cholestrol Raised cholestanol levels	Chenodeoxychol ic acid, HMG CoA reductase inhibitors
Infantile onset spinocerebellar ataxia (IOSCA)	C10orf2 (Reduced function of Twinkle protein Mitochondrial DNA depletion)	Peripheral neuropathy, epilepsy, athetosis, optic atrophy, deafness, ophthalmoplegia, primary hypogonadism in females	Cerebellar and brainstem atrophy[16] Mutation studies	
Marinesco - Sjogren syndrome	SIL1	Cataract, hypotonia, hypogonadism, kypho scoliosis, myopathy, intellectual disability	Cerebellar atrophy	

Table VI. Clues from history

Symptoms	Disease
Acute onset in an unsupervised toddler	Drugs, toxins
Recurrent or persistent headache, vomiting, diplopia	Posterior fossa space occupying lesion
H/O trauma, fall	Concussion, posterior circulation stroke
Fever, rash, gastrointestinal illness/ recent immunization	ADEM, acute cerebellar ataxia, Miller Fisher variant of GBS
Self-limiting episodes, family history	Episodic ataxias type 1-7
Normal in between the attacks, intermittent ataxias precipitated by infections, drugs	Metabolic (amino acidopathies, urea cycle disorders, organic acidemias, mitochondrial cytopathies)
Encephalopathy	ADEM, drug toxicity
Dizziness	Benign paroxysmal vertigo, stroke, migraine

Table VII.Clues from general examination

Clinical clue	Disorders
Short stature	Mitochondrial, ataxia telangiectasia
Telangiectasia	Ataxia telangiectasia
Cataract	Marinesco Sjogren, cerebrotendino xanthomatosis
Deafness	Friedrich's ataxia, Refsum disease, mitochondrial
Icthyosis	Refsum disease
Tendon xanthomas	Cerebro tendino xanthomatosis
Spine /foot deformity	Friedrich's ataxia, ataxia with vitamin E deficiency (AVED)

Table VIII. Clues from neurological signs apart from ataxia

Neurological signs	Disease
Ataxia with oculomotor apraxia	Ataxia telangiectasia, AOA1, AOA2
Ataxia with peripheral neuropathy	Friedrich's ataxia, ataxia with vitamin E deficiency (AEVD), Refsum disease, abetalipoproteinemia, late onset Tay-Sachs disease
Ataxia with cognitive dysfunction	Cerebellar malformations, mitochondrial diseases, ataxia telangiectasia, neuronal ceroid lipofuscinosis, inborn errors of metabolism

Table IX. Diagnostic tests to be done in ataxic children

Investigation	Indications / findings
Urine and/or serum toxin screening	In all cases of acute or intermittent ataxia
Neuro imaging - CT or MRI brain	Posterior fossa tumours Hypoplasia of vermis and or cerebellar hemispheres in congenital ataxias Molar tooth appearance and key hole IV ventricle in Jouberts syndrome Herniation of cerebellar tonsils and medulla in Chiari malformation Posterior fossa cyst communicating with IV ventricle in Dandy Walker malformation Usually normal in acute cerebellar ataxia Multiple asymmetrical foci of demyelination in cerebellum, basal ganglia, cerebrum in ADEM Infarcts, haemorrhage in vascular causes Cerebellar atrophy in ataxia telangiectasia, AOA1, AOA2, hypoxia Normal cerebellum in Friedrichs, abetalipoproteinemia, AVED, Refsum's disease
MR angiography, venography CT/MRI abdomen, chest	In posterior circulation strokes To rule out neuroblastoma in opsoclonus myoclonus syndrome
Cerebrospinal fluid examination	Usually normal in acute cerebellar ataxia Mild pleocytosis and elevation of protein in ADEM Cyto albumino dissociation in Miller Fisher variant

Investigation	Indications / findings
Electro physiology	Nerve conduction studies to rule out associated peripheral neuropathies in inherited ataxias Visual evoked potentials in demyelinating disorders (ADEM); ECG, ECHO in Friedrich's ataxia, mitochondrial disorders
Genetic testing	GAA repeats in Friedrichs ataxia, mutation in ATM gene in Ataxia telangiectasia
Metabolic workup	Lactate, pyruvate, ketones, ammonia, serum amino acids, urine organic acids in episodic ataxias to rule out inborn errors of metabolism
Urine catecholamines (metanephrines, vanillylmandelic acid)	In opsoclonus myoclonus syndrome
Serum isoelectric focusing	In congenital disorders of glycosylation (CDG)

Table X. Biomarkers associated with autosomal recessive ataxia[4]

Biomarkers	Abnormality	Disease
Acanthocytes	Present	Abetalipoprotenemia
Albumin	Reduced	AOA1
Álpha feto protein	Elevated	Ataxia telangiectasia, AOA2
Cholestanol	Elevated	Cerebro tendino xanthomatosis
Hexosaminidase	Reduced	Late onset Tay-Sach disease
Immunoglobulins	Reduced	Ataxia telangiectasia, AT like disorder
Lactate	Elevated	Autosomal recessive cerebellar ataxia
Radiosensitivity	Present	Ataxia telangiectasia, AT like disorder
Very Long Chain Fatty Acids	Elevated	Refsum disease
Vitamin E	Reduced	Abetalipoproteinemia, Ataxia associated with Vitamin E deficiency

pyramidal tract, extrapyramidal system, peripheral nerves, ophthalmoparesis and deafness would help to delineate the etiology. Detailed sensory examination is needed to rule out sensory ataxia. Particular attention is needed for joint, position, vibration sense examination and Romberg's sign.

Investigations

Evaluating the child with ataxia requires a practical systematic and comprehensive approach so that treatment, if available, can be instituted as expediently as possible. The workup requires careful planning to maximize patient and clinical resources. The relevant investigations and their significance are depicted in (Table IX).

Because replacement or dietary therapies can be clinically valuable in many of these cases, biomarker testing is essential in young children prior to genetic testing (Table X). [4,15]

The flowchart (Fig.2) summarizes the clinical and laboratory approach to a child with ataxia.

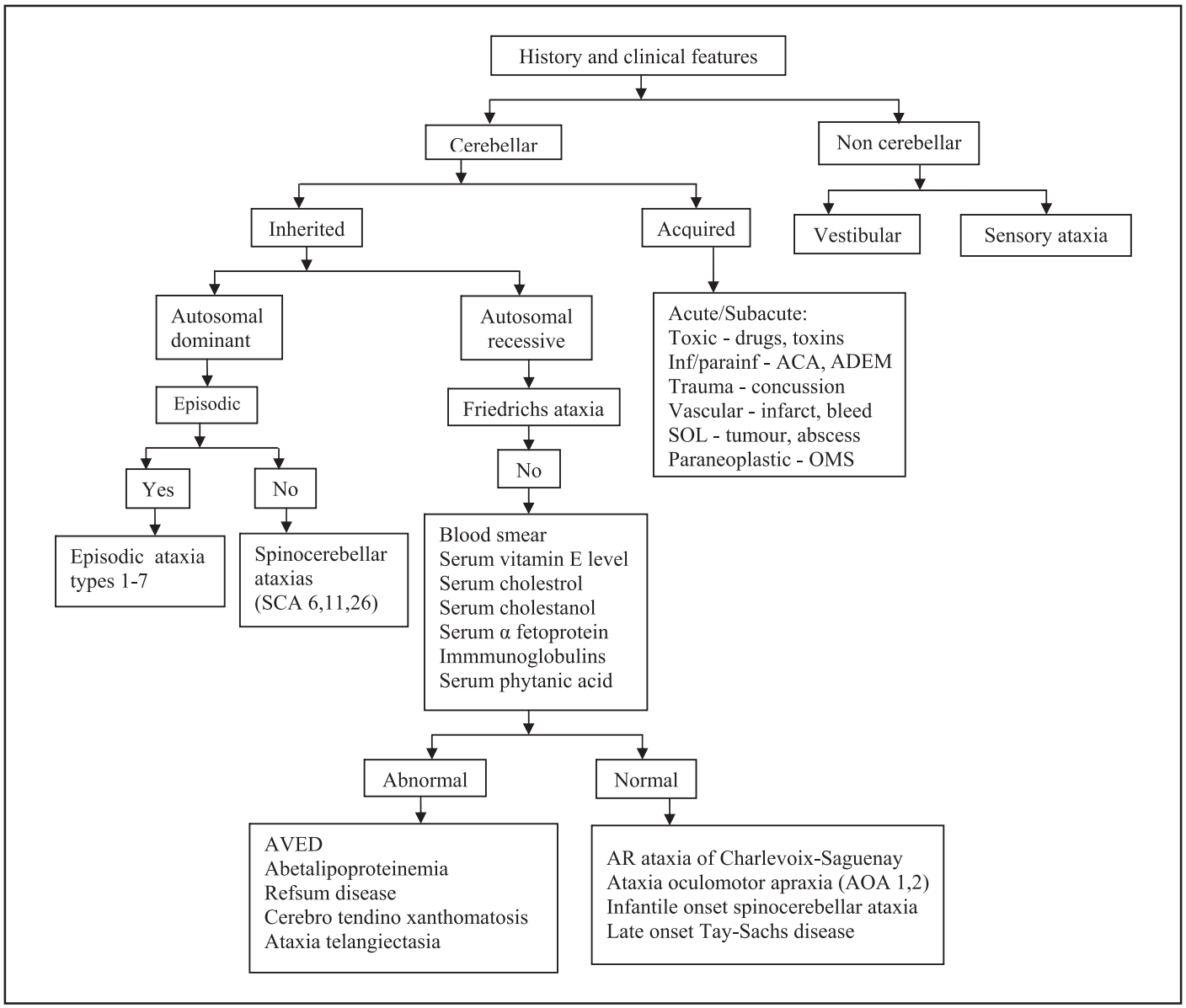

Fig.2. Clinical approach in a child with ataxia

Points to remember

- ***Ataxias in children may be a manifestation of wide range of disorders.***
- ***Diagnosis should be approached with a chronological order into acute, intermittent, and chronic ataxia.***
- ***Acute cerebellar ataxia is the most common cause of childhood ataxia which usually results from drug ingestion or postinfectious cerebellar demyelination.***
- ***Intermittent ataxia should raise the suspicion of an underlying inborn error of metabolism.***
- ***Friedrichs ataxia followed by ataxia telangiectasia are the common causes of inherited ataxias in children.***

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CLIPPINGS

Video laryngoscopy vs. direct laryngoscopy: Which should be chosen for endotracheal intubation during cardiopulmonary resuscitation?: A prospective randomized controlled study of experienced intubators.

This study compared endotracheal intubation (ETI) performance during cardiopulmonary resuscitation (CPR) between direct laryngoscopy (DL) and video laryngoscopy (VL) by experienced intubators. Total 140 ETIs by experienced intubators using DL (n=69) and VL (n=71) were analysed. There were no significant differences between DL and VL in the ETI success rate (92.8% vs. 95.8%; p=0.490), first-attempt success rate (87.0% vs. 94.4%; p=0.204), and median time to complete ETI (51 [36-67] vs. 42 [34-62]s; p=0.143). In both groups, oesophageal intubation and dental injuries seldom occurred. However, longer chest compressions interruption occurred using DL (4.0 [1.0-11.0]s) compared with VL (0.0 [0.0-1.0]s) and frequent serious no-flow (interruption>10s) occurred with DL (18/69 [26.1%]) compared with VL (0/71) (p<0.001). For highly experienced intubators (>80 successful ETIs), frequent serious no-flow occurred in DL (14/55 [25.5%] vs. 0/57 in VL).

The ETI success, speed and complications during CPR did not differ significantly between the two devices for experienced intubators. However, the VL was superior in terms of completion of ETI without chest compression interruptions.

Kim JW, Park SO, Lee KR, Hong DY, Baek KJ, Lee YH, et al. Video laryngoscopy vs. direct laryngoscopy: which should be chosen for endotracheal intubation during cardiopulmonary resuscitation?: A prospective randomized controlled study of experienced intubators. Resuscitation, April 2016. pii: S0300-9572(16) 30014-4. doi: 10.1016/j.resuscitation.2016.04.003. [Epub ahead of print].

NEWS AND NOTES

9th National Conference of IAP Neonatology Chapter, Ranchi

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PEDIATRIC NEUROLOGY

PEDIATRIC CNS DEMYELINATING DISORDERS- AN UPDATE

***Lokesh Lingappa**
****Nikit Milind Shah**

Abstract: *Pediatric central nervous system (CNS) demyelinating disorders are a heterogeneous group of conditions with demyelination as the pathological hall mark, acute demyelinating encephalomyelitis (ADEM) being the commonest disorder with very good long term outcomes. Optic neuritis has variable outcome despite aggressive treatment. Transverse myelitis is the most severe of all the demyelinating disorders due to the long term disability it produces. Multiple sclerosis is well known to have a relapsing or progressive course.*

Keywords: *Demyelinating disorders, Central nervous system, Children.*

CNS demyelinating disorders are a varied spectrum of conditions with overlapping presentations along with typical neuroradiologic findings. It is very important to diagnose these conditions as they have specific treatment with good outcomes. Purpose of this review is to describe the spectrum of CNS demyelinating disorders in children and adolescents with clinical and radiological differences. De-myelination is usually an acute or acute relapsing process as compared to dysmyelination which is chronic process and can be radiologically differentiated with contrast MRI and natural course. Scope of this review includes acute disseminated encephalomyelitis (ADEM), acute nectrozing encephalitis (ANE), clinically isolated syndrome (CIS), multiple sclerosis (MS) and neuromyelitis optica (NMO) spectrum disorders along with controversial aspects, diagnostic problems and a note about future trends.

Acute demyelinating encephalomyelitis (ADEM)

ADEM is an inflammatory disorder usually preceded by either febrile illness such as upper respiratory infections and diarrheal illness or certain vaccines. It is classically described as a monophasic illness but also can be multiphasic[1] (not fulfilling criteria for MS) or evolve into a spectrum of demyelinating disorders. Basic pathogenesis in these disorders is inflammation of CNS with subsequent demyelination hence most physicians treat it with short course steroids. Classic clinical manifestation is encephalopathy or altered sensorium already with other symptoms such as seizures, limb paresis etc. Optic neuritis and myelitis may be seen.[1] Brainstem involvement presents with features of brainstem encephalitis.

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Epidemiology

ADEM affects children with the incidence rate of 0.4 - 0.8/100000 yearly among children less than 20 years old.[2,3] The peak incidence of ADEM is among 5 to 8 years of age.[3] There is no sexual predilection. There is increased incidence during winter and spring season.

Definition

Following definition is suggested by international pediatric multiple sclerosis society (IPMS) in 2007 for various forms of ADEM.[4]

Monophasic ADEM

(1) A first clinical event with a presumed inflammatory or demyelinating cause, with acute or subacute onset that affects multifocal areas of the CNS. The clinical presentation must be polysymptomatic and must include encephalopathy (defined as behavioral change or alteration in consciousness).

(2)MRI shows focal or multifocal lesions(s), predominantly involving white matter, without radiological evidence of previous destructive white-matter changes (Fig.1).

New or fluctuating symptoms, signs, or MRI findings occurring within 3 months are considered part of the acute event, and are diagnosed as ADEM.

Recurrent ADEM

(1) A new event of ADEM (fulfilling ADEM criteria above), with recurrence of the initial symptoms and signs, 3 or

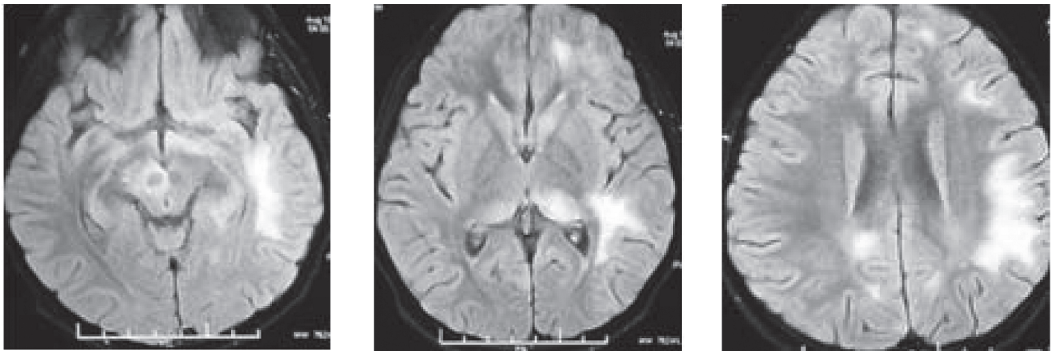

Fig. 1. ADEM- Axial FLAIR images showing polyfocal white matter lesions involving a) cerebral peduncle, b) bilateral thalamus c) subcortical white matter

more months after the first ADEM event, without involvement of new clinical areas.

(2) The event does not occur while the patient is on steroids, and occurs at least one month after completing therapy.

(3) MRI must show no new lesion although original lesions may have enlarged.

(4) There should be no other explanation for the event.

Multiphasic ADEM (MDEM)

(1) ADEM followed by a new clinical event also meeting criteria for ADEM (i.e. must have encephalopathy), but involving new anatomical areas of the CNS as confirmed on history, examination, and neuroimaging.

(2) The subsequent event must occur at least 3 months after the onset of the initial ADEM event and at least 1 month after completing steroid therapy.

(3) The subsequent event also must include a polysymptomatic presentation and include encephalopathy.

(4) Brain MRI must show new areas of involvement but also complete or partial resolution of the first ADEM event lesions.

Pathogenesis

ADEM is described classically as post-infectious autoimmune process with a possible mechanism described as molecular mimicry; but also can occur as para-infectious disorder. Experimental data suggests that secondary autoimmune response as well as immune response to direct microbial invasion causes inflammation and subsequent demyelination. Two experimental animal models have been proposed.

The inflammatory cascade concept[5]: Direct CNS infection with a neurotropic pathogen, results in CNS tissue damage and systemic leakage of CNS-confined auto antigens through a disintegrated blood-brain barrier. These antigens, once processed will lead to tolerance breakdown and to a self-reactive T-cell response. Such activated T cells are capable of invading the CNS and perpetuating CNS inflammation and demyelination.

The molecular mimicry concept[5]: Partial amino-acid sequence homology is seen between the inoculated pathogen and myelin proteins of the host. Antigen-presenting cells such as dendritic cells process the pathogen at the site of inoculation, leading to T-cell activation. Activated T cells may in turn cross-activate antigen-specific B cells. Both activated T cells and B cells are quite capable of entering the CNS for immune surveillance. Thus, even after clearance of the pathogen, these antigen-specific cells may encounter the homologue myelin protein during their physiologic surveillance of the CNS. They may become reactivated by local antigen-presenting cells such as microglia, causing an inflammatory immune reaction against the presumed foreign antigen.

Vaccine induced ADEM[5]: Vaccine-associated ADEM cases can be directly attributed to the contamination of the specific vaccine with CNS tissue. This contamination may explain the substantial 0.15% incidence of ADEM after immunization with a live attenuated rabies virus vaccine (Semple vaccine) in developing countries, which is propagated in cultures of rabbit or goat CNS tissue. Incidence of ADEM with this vaccine was 1 in 400 vaccinees. With development of tissue culture vaccines and human diploid cell vaccine, the incidence has significantly reduced. Similar trends were observed with Japnese B encephalitis vaccine which was propagated in mouse brain. Other viruses for attributed acute demyelination are hepatitis B, measles, mumps, rubella, pertussis, polio, tetanus etc in various case reports.[5]

Pathology

The pathological hallmark of ADEM is perivenular inflammation with limited sleeves of demyelination. Larger areas of demyelination occur secondary to coalescence of many perivenous demyelinating lesions. Although perivascular inflammation is also a feature of MS pathology, the patterns of demyelination in ADEM stand in contrast to the confluent sheets of macrophage infiltration admixed with reactive astrocytes in completely demyelinated regions that are typical of an MS plaque.[1] The clinical characteristics of patients with biopsy-proven confluent demyelinating disease (excluding patients with perivenous demyelination) were found to be similar to a population-based MS cohort. It is unknown whether a perivenous pattern of demyelination predicts a monophasic course or whether the presence of confluent demyelination predicts future relapse.[6]

Clinical features

Clinical symptoms start within days to weeks of preceding infection.

1. Encephalopathy: This is the key symptom due to involvement of various areas like bilateral thalamus, reticular activating system in brainstem (Fig.2) or diffuse cortical involvement. Encephalopathy also can be there as part of infectious encephalitis which needs to be differentiated from para-infectious ADEM. Persistent encephalopathy and subacute progression favors more for ADEM like illness where as infectious encephalitis will have explosive onset and then slow recovery. Encephalopathy may be mistaken for postictal state. Aphasia due to focal demyelination in posterior frontal area, visual symptoms due to parieto-occipital involvement and frontal behavioral syndrome can be seen. One of the key findings in these children is significant mismatch between the lesion load on the MRI and clinical features. Children look less severely involved clinically for the degree of neuroimaging lesions. Cerebrospinal fluid analysis also helps in differentiating infectious from demyelinating process.

2. Other neurological symptoms and signs[7]:a) Hemiplegia (76%), b) ataxia (18-65%), c) cranial nerve palsy (22-45%), d) visual impairment due to optic neuritis (7- 23%), e) seizure (13-35%), f) headache, g) spinal cord involvement (24%), h) speech impairment (5-21%), i) bladder and bowel dysfunction secondary to spinal cord involvement, j) pyramidal signs (60-95%), k) eye movement abnormalities / ophthalmoplegia

3. Recovery can begin within days; on occasion complete resolution is noted within a few days, but more frequently occurs over the course of weeks or months. The mortality varies between 10% and 20%, with complete recovery in 50%. Poor prognosis is correlated with severity and abruptness of onset of the clinical syndrome.[8]

Investigations

EEG: It gives nonspecific information. Main role of EEG is to rule out nonconvulsive status epilepticus which can present as acute encephalopathy.

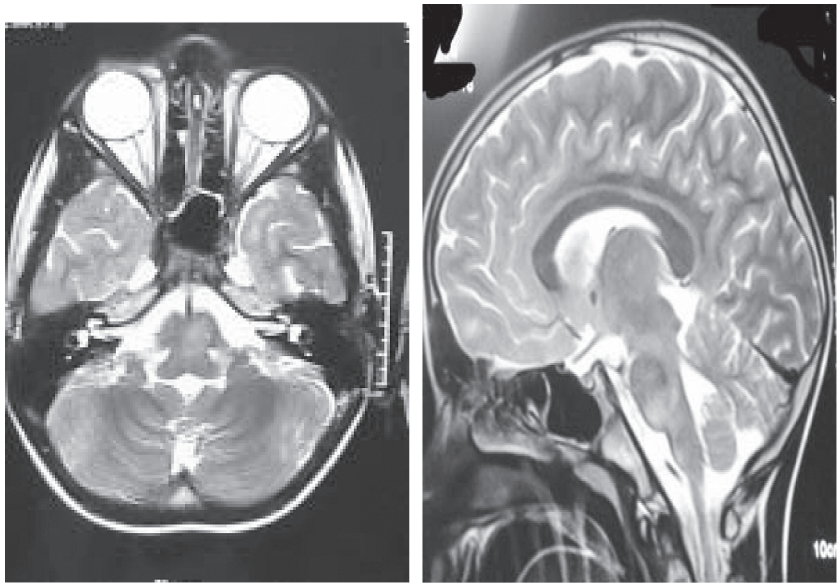

Fig. 2. Brainstem ADEM-Axial(a) and sagittal(b) T2W images showing signal changes in midbrain and medulla

CSF analysis: Lumbar puncture must always be performed to rule out acute infective encephalitic process

The cerebrospinal fluid (CSF) may show: a) Nonspecific lymphocytic pleocytosis (because of inflammatory response); up to 1000 cells/cumm have been reported; may occasionally have initial neutrophilic response; pleocytosis will be rarely seen in MS.[8] b) Elevation of protein levels (because of demyelinating process near the CSF spaces); median frequency of oligoclonal band in childhood cases was 12.5% (range, 0-29%) and higher in the adult cases (37.558%). Production of oligoclonal IgG almost always stops as patient improves and would continue to occur in MS.[5] c) CSF PCR studies in children with doubtful features of ADEM on MRI or if CSF pleocytosis is more than 100cells/ml.

MRI brain: This is a key investigation for diagnosis of any suspected CNS demyelinating disease accompanied by MRI spine as and when required. International society for multiple sclerosis diagnostic criteria is based on imaging findings. Imaging changes would be classically seen between 4 -14 days and hence early neuroimaging would sometimes be negative. CT brain would be of limited help unless quick imaging is required for ruling out space occupying lesions in a sick ventilated child. MRI demonstrates areas of signal changes as increased signal on T2W and FLAIR sequence and areas of low signal on T1W images. FLAIR images are of great help in characterizing lesions and classifying them. Diffusion weighted images (DWI) may show restricted diffusion occasionally. Most of the times diffusion weighted images are normal.

Characteristics of ADEM lesions on MRI

1. Areas involved: White matter tracts of brain, bilateral thalami, brainstem, cerebellum, bilateral / unilateral optic nerves, spinal cord
2. Areas spared: Corpus callosum and periventricular white matter is typically spared in ADEM and its involvement is usually suggestive of multiple sclerosis
3. No mass effect but there can be mild perilesional edema
4. Patchy, blotchy, poorly marginated and multiple areas of increased signal on T2W and FLAIR are seen
5. All lesions are of same age on MRI (same signal intensity).
6. Sometimes there might be single large lesion (coalescence of multiple small lesions) with central necrosis typically described as Tumefactive necrosis with demyelination and may mimic tumors like astrocytoma (Fig.3)
7. Few lesions may enhance on gadolinium
8. Bilateral thalamic involvement is extremely common in children with ADEM (40%) and would be theoretically absent in MS (Fig.4)
9. Occasionally grey matter involvement may be seen

Treatment

Mainstay of treatment in all inflammatory demyelinating illnesses is steroids. High dose intravenous steroids (methylprednisolone 30 mg/kg/day, max 1gm/day)

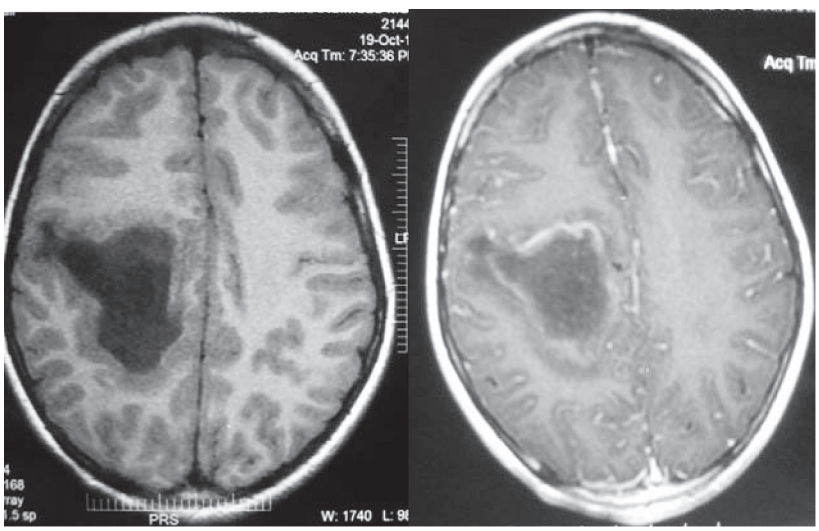

Fig. 3. Tumefactive demyelination- Axial T1 plain(a), Axial and (b) post contrast images showing cystic white matter lesion with partial ring peripheral contrast enhancement.

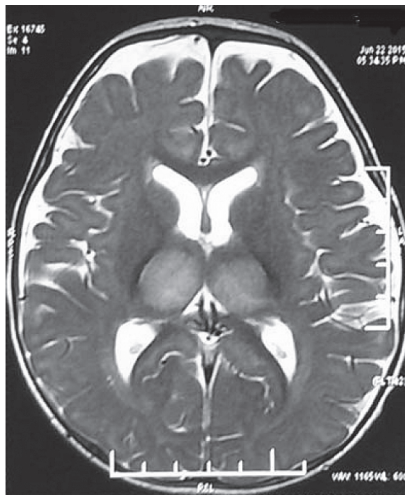

Fig.4. Bilateral Thalamic ADEM- Axial T2W images showing increased signal in bilateral thalami

followed by 4-6 weeks of oral steroids form the start of treatment. Shorter duration of steroids is associated with increased relapse rate. Other described modalities of treatment are intravenous immunoglobulins and plasmapheresis. Sometimes newer immune modulators like rituximab (anti CD 20) may be used for MDEM. Second and third line immunomodulation has to be decided on case to case basis.

Prognosis

Factors associated with increased risk of MS after 1st episode of demyelinating illness[9,12]

1. Age > 10 years
2. No prodromal illness
3. Absence of encephalopathy (clinically isolated event)
4. Presence of oligoclonal band / increased IgG index
5. Monofocal presentation (eg., unilateral optic neuritis)
6. Presence of periventricular perpendicular ovoid lesions
7. Presence of unusual demyelinating focus like spinal cord and unilateral optic neuritis
8. Non-symptomatic lesions

Acute necrotizing encephalitis

Acute necrotizing encephalopathy of childhood (ANEC) is an atypical encephalopathy seen almost exclusively in previously healthy young children or infants of East Asia including Japan and Taiwan. However sporadic and familial cases have been reported from all around the world. It was first described in Japan by Mizuguchi and

Table I. Differential diagnosis according to MRI lesions

Multifocal discrete lesions (Fig.1)	Multiple sclerosis Primary CNS vasculitis Secondary CNS vasculitis (CNS lupus, Behcet's) Neuro sarcoidosis Mitochondrial; MELAS Posterior reversible encephalopathy
Bithalamic/bistriatal lesions (Fig.4)	Acute necrotizing encephalopathy Mitochondrial; POLG-related disorders Mitochondrial; Leigh's disease Deep cerebral vein thrombosis Extrapontine myelinolysis Japanese encephalitis Dengue encephalitis West Nile virus encephalitis Ebstein Barr virus encephalitis
Bilateral, diffuse large white matter lesions	Leukodystrophies Toxic leucoencephalopathy Hemophagocytic lymphohistiocytosis Juvenile xanthogranulomatosis (rare)
Tumefactive lesions (Fig.3)	Astrocytoma Brain Abscess

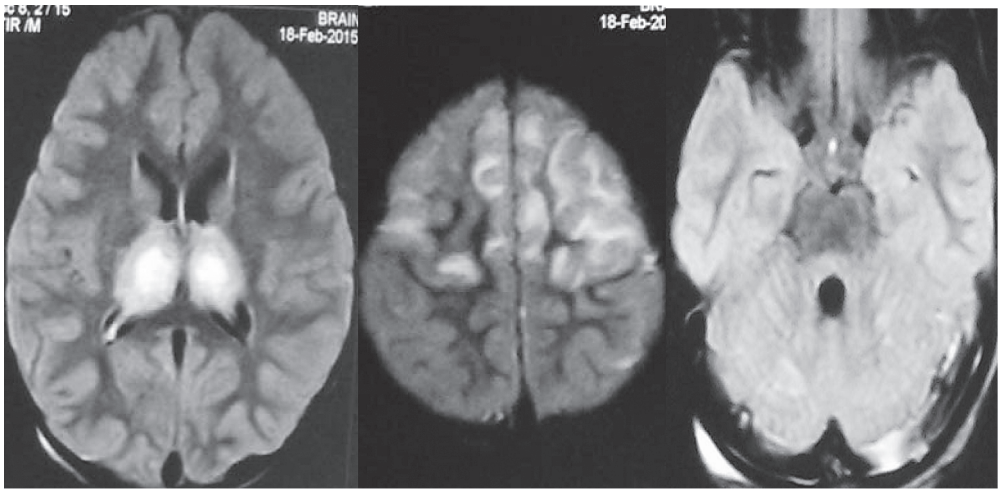

Fig.5. Acute Necrotising Encephalitis- Axial FLAIR image showing (a) bithalamic, (b) supratentorial white matter and (c) cerebellar white matter signal changes with necrotizing thalamic lesion

Colleagues in 1995.[10] Acute necrotizing encephalopathy (ANEC) is a clinical and neuroradiologic entity.

Etiopathogenesis

The etiology of ANEC is unknown. It is described as postinfectious process after many common virus infections like influenza, parainflienza, herpes 1,2, measles, rubella, varicella, enterovirus, rotavirus etc. However influenza A virus, mycoplasma, HSV and HHV-6 have been implicated as common causative agents, directly or through an immune-mediated mechanism. Pathophysiology implicated is "Cytokine storm theory".[11] Hypercytokinemia secondary to CD 56+ NK cell activation leads to systemic symptoms and increase in capillary leak and breakage of blood brain barrier leading to necrosis and hemorrhage. Surprisingly despite intense inflammation and necrosis CSF analysis is normal. Notably, pathologic brain specimen shows minimal inflammation in relation to extensive parenchymal abnormalities.

Infection-induced acute encephalopathy-3 (IIAE3) is caused by heterozygous mutation in the RANBP2 gene on chromosome 2q11-q13. It is inherited in an autosomal dominant pattern. A missense mutation in RANBP2 is a genetic risk factor for an environmentally triggered neurologic disease. The hallmark of this encephalopathy consists of multifocal, symmetric brain lesions affecting the bilateral thalami and/or cerebral periventricular white matter, brainstem, tegmentum or cerebellar medulla (Fig.5). According to Mizuguchi et al, the localized edema, congestion or hemorrhage were more severe in the center of thalamus than the periphery giving the concentric appearance on imaging.[10]

Clinical profile[11]

1. Severe neurologic complication after a mild viral illness (Prodromal phase).
2. Previously healthy child rapidly progresses to having seizures and profound coma (encephalopathic stage).
3. Systemic signs: Acute transaminitis, lactic acidosis, hypoglycemia, thrombocytopenia, disseminated intravascular coagulopathy (DIC).
4. Stage of recovery: Outcomes are diverse including mild disease with complete recovery to severe neurological sequelae and death.
5. Radiology: Bilaterally symmetric lesions in the thalamus with central necrosis and / or hemorrhage can point to the diagnosis early in the course of this illness. Other areas involved with disease process are cerebral white matter, cerebellar white matter and brainstem.

Treatment and outcomes

Immunomodulatory interventions, antiviral medication and metabolic supplementation as indicated may be tried. Although there has been a suggestion that early intervention may ameliorate clinical outcome, it remains unclear whether early and aggressive therapy can eliminate neurologic sequeale of this disease. It is hoped that genetic discoveries will lead to more targeted and successful treatment options in the future. The long term outcome of this condition is rarely encouraging. In conclusion, recurrent or familial disease and an expanded clinical and radiological phenotype point towards ANE and

should prompt genetic analysis; currently mutation analysis may be advisable in all patients with ANE to further determine genotype–phenotype correlations.

Multiple sclerosis / MS

Multiple sclerosis is a disorder of adolescents and young adults. It is rare in pediatric age group and incidence ranges from 3-5 % of total MS patients. Children less than 10 years age comprise < 1% of total MS population. Overall incidence of MS in pediatric age is unknown. In large population based studies in California incidence reported is 0.5 per 1,00,000 people year. Overall the incidence of first episode of acute demyelinating diseases 1st episode ranges from 0.6 to 0.9/ 1,00,000 people.[12] This makes MS as rarest demyelinating disease in childhood. First episode of MS may present as ADEM but there are key differences which differentiate first episode of MS from ADEM though there might be overlap and sometimes difficulty[4] to differentiate. Key differentiating symptom is encephalopathy which is present in 69% of ADEM and 15 % of MS in one study.[13] Other differentiating features are described in table II.

Epidemiology

A reliable statistics on prevalence or incidence of pediatric MS is still unknown. The estimated incidence is between 0.3 and 0.5/100,000 children. However, these figures are derived from studies that are not nationwide and prospective. It appears to be significantly more frequently seen in Caucasian population as compared to Asian population. Overall increased female preponderance is observed especially after 10 years of age. In children younger than 10 years, the female-to-male ratio is about equal. About 8% of children with MS have a family history of MS.[9]

Criteria for the diagnosis of MS are given in Box.1.

Revised McDonald's criteria[14]

*Disseminated in space (DIS): >One T2 bright lesions in 2 or more of following areas[a]: Periventricular, juxtracortical, infratentoreal, spinal cord [b]

a. Gadolinium enhancement of lesions is not required for DIS.

b. If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and do not contribute to lesion count.

Box 1. Criteria for the diagnosis of MS (any one of following)[4]

1. Two or more nonencephalopathic (e.g. not ADEM-like), clinical CNS events with presumed inflammatory cause, separated by more than 30 days and involving more than one area of the CNS
2. One non-encephalopathic episode typical of MS which is associated with MRI findings consistent with 2010 Revised McDonald criteria for disseminated in space (DIS)* and in which a follow up MRI shows at least one new enhancing or nonenhancing lesion consistent with 'disseminated in time (DIT)[$]' MS criteria.
3. One ADEM attack followed by a nonencephalopathic clinical event, three or more months after symptom onset, that is associated with new MRI lesions that fulfill 2010 Revised McDonald DIS criteria
4. A first, single, acute event that does not meet ADEM criteria and whose MRI findings are consistent with the 2010 Revised McDonald criteria for DIS and DIT (applies only to children ≥ 12 years old)

[$]Disseminated in time (DIT) (1of 2)

New gadolinium enhancing lesions when compared to previous imaging (irrespective of time); Presence of asymptomatic gadolinium enhancing lesion and a non enhancing T2 lesion on any scan.

Pathophysiology

Perivascular infiltrates are specific for multiple sclerosis. Confluent sheets of macrophage infiltration admixed with reactive astrocytes in completely demyelinated regions that are typical of an MS plaque. As with other autoimmune diseases, cause for demyelinating event in MS is unknown as against in ADEM where possible underlying mechanisms have been proposed. Current evidence describes complex interplay of genetic predisposition and environmental exposure. Still it is undetermined what possibly triggers onset and relapses. Genetic variation in certain genes involved in immune mechanisms and major histocompatibility complex may have a role.[12]

Association between remote EBV infection and increased incidence of MS in adults has been documented in some studies.[9]

Clinical features[15]: These are listed in Box 2.

Box 2. Clinical features in MS

1. Same as ADEM except encephalopathy (may be seen rarely)
2. Polyfocal presentation (50-70%)
3. Monofocal presentation (30-50%)
4. Fatigue (40%)
5. Optic neuritis (usually unilateral) (10-22%)
6. Motor dysfunction (30%)
7. Sensory symptoms (15-30%)
8. Ataxia (5-15%) (more common in younger children)
9. Brainstem symptoms (25%) (rare in younger children)
10. Isolated transverse myelitis (< 10%)
11. Seizures (< 5%) (common under age of 10 years)
12. Encephalopathy (20-30%) (common in young children)
13. Multiphasic disease with dissemination in time and space as described in 2010 McDonalds modified criteria
14. Deficits in cognition, visuomotor coordination, and memory (30%)

Diagnostic evaluation

A) Neuroimaging: (MRI brain is the key investigation)

Various criteria have been proposed for differentiating first attack of MS from ADEM or clinically isolated syndrome.[9]

McDonald MRI criteria (3 out of 4)

≥ 9 lesions on T2-weighted imaging

≥ 3 periventricular lesions

≥ 1 juxtacortical lesion

≥ 1 infratentorial lesion

B) CSF analysis

Persistent CSF oligoclinal band (> 2 documented CSF values) or elevated IgG index is definitive finding in MS against ADEM where oligoclonal band disappear during resolution. It may also help in differentiating other infections diseases. In some cases, the oligoclonal bands initially can be negative and detected only later in the course of the disease.

C) Neurophysiology studies

Visual evoked potential (VEP) - An abnormal VEP with prolonged P100 latency in clinically unaffected eye would an evidence of dissemination in space.

SSEP(somatosensory evoked potentials)- is another potential tool to evaluate asymptomatic spinal cord involvement in MS

The differentiating features between ADEM and MS are shown in Table II.

Treatment

The care of children with MS needs a multidisciplinary team comprising pediatric and adult neurologist, nurse,

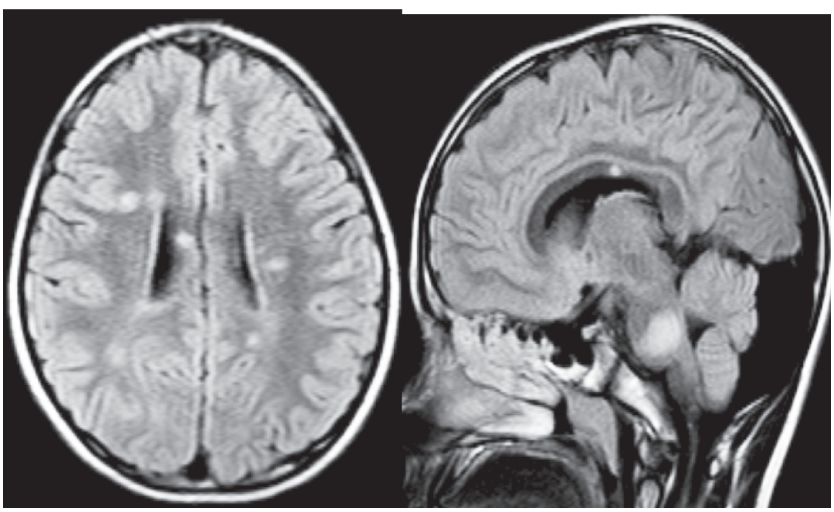

Fig.6. Multiple sclerosis- (a) FLAIR Axials demonstrating multiple plaque-like hyperintense lesions involving the periventricular white matter (b) Sagittal FLAIR image showing signal change(well defined small ovoid lesion) in corpus callosum and large well defined lesion in pons

Table II. Differences between ADEM and MS

	ADEM	MS
Age	<10 years	> 10 years
Sex	Slight male predominance	Female predominance
Presentation	Usually polyfocal	Usually monofocal
Prodromal phase	+	-
Encephalopathy	+	-
Seizure	+	-
Ataxia	More common	Less common
Optic neuritis	Bilateral	Unilateral
Spinal cord involvement	Less common	More common
MRI characteristics		
Bithalamic lesions	+	-
Corpus callosal lesion	-	+
Peri focal edema / mass effect	+	-
Multistage lesions	-	+
Asymptomatic lesions	-	+
Followup MRI	Complete resolution / Gliosis	New lesions and black holes
CSF	Oligoclonal band (uncommon)	Oligoclonal band (common)

physiotherapist, occupational therapist, social worker, psychologist, and psychiatrist.

Management of acute attack of demyelination is high dose pulse methylprednisolone (30 mg/kg/day) for 3-5 days followed by oral prednisolone 1-2 mg/kg/day with tapering for total 6 weeks; depending on need after pulse dose.[15] Milder non disabling attacks do not require steroids. Children who do not respond to first course of pulse methylprednisolone can be given second course of steroids for another 3-5 days. For children in whom corticosteroid therapy is contraindicated or ineffective, treatment with intravenous immunoglobulin (IVIg) might be of value (class IV evidence) in a dose of 2 g/kg over 2–5 days. There is evidence for the benefit of plasma exchange for life-threatening demyelination in adults who do not respond to corticosteroids (Class I); and typically 5-8 exchanges can be performed.

Immunomodulatory therapy[9,15]

Based on the evidence of reduction in the relapse frequency in adults with MS (Class I) interferon beta and glatiramer acetate are used in children. None of theimmunomodulatory therapies has been formally assessed in large clinical trials of children. Second line drugs include natalizumab and fingolimod. The number of children treated with natalizumab is increasing. Limited numbers of reports are available of its effectiveness. Safety profile of natalizumab is not completely described in children. Other immunomodulators like rituximab, mitoxantron, cyclophosphamide, teriflunomide and dimethyl fumarate (BG-12) are not used in children in view of scarcity of pediatric data though they have been approved by the FDA for use in adults with MS.

Prognosis[9]

It is important to identify MS early in the course as treatment started early during the course may alter the outcome. Almost all children have relapsing and remitting

course. Children have high initial relapse rate but better recovery due to better brain repairing capacity as compared to adults. Younger children tend to have a longer interval from first to second attack (median 6 years), in contrast to most adolescent patients with MS, who have their second attack within 12 months. More than 31% of the children with MS have a decrease in cognitive functioning in the first years of their disease, irrespective of disability status and number of relapses. The occurrence of cognitive impairment early in the disease course may be explained by the interference with processes of CNS myelination and maturation of neuronal networks. Cognitive decline, depression, frequent school absences, chronic relapsing disease course, chronic fatigue, treatment complications and familiar disharmony can occur in children with MS.

Female sex, well-defined lesions perpendicular to the corpus callosum on MRI and secondary-progressive disease are predictions of severity of MS.

Neuromyelitis optica (NMO) spectrum disorder

Neuromyelitis optica (NMO) was previously known as Devic's disease. Previously it was considered as variant of MS as it shares pathophysiology and areas involved. NMO spectrum disorder (NMOSD) involves optic nerve, periaqueductal grey matter and spinal cord. Involvement of these areas is extensive as compared to MS. Identification of aquaporin 4 (CNS astrocyte water channel) autoantibodies has made breakthrough and gave NMO a separate identity. It detects NMO with 100% specificity and is positive in 60% of spectrum patients.

Other variants of NMO are now recognized

a. Relapsing optic neuritis (ON)
b. Severe and bilateral ON
c. Longitudinally extensive tranverse myelitis (LETM)
d. Asian optico-spinal MS
e. ON or LETM associated with systemic autoimmune disease.

Epidemiology: NMO occurs in about 3.2-8.5% of all children with demyelinating disorders. The mean age of disease-onset lies between 10-14 years. It occurs more often in females and in non-white children, like Afro-Americans and Asians.[9]

Definition: International panel for NMO diagnosis (IPND) 2014 revised criteria (all required)

a. Optic neuritis
b. Acute myelitis
c. At least two of three supportive criteria:
    - Contiguous spinal cord MRI lesion extending over three vertebral segments also known as 'Longitudinally extensive transverse myelitis (LETM)'
    - Brain MRI not meeting diagnostic criteria for MS
    - Anti-aquaporin-4 (AQP4) IgG seropositive status

Pathogenesis: Pathologic findings in biopsy or autopsy tissue obtained from patients with AQP4-IgG-seropositive NMOSD demonstrate loss of AQP4 immunoreactivity and evidence of perivascular complement activation in actively demyelinating lesions. These findings in active lesions distinguish AQP4-IgG positive NMOSD from MS. Data from seronegative individuals are not yet available. Necrosis and lesion infiltration with neutrophils and eosinophils are supportive characteristics.

Clinical features[16]

1. Optic nerve involvement: Visual impairment can be unilateral or bilateral. Unilateral visual loss is often compensated and does not usually manifest unless it progresses to bilateral loss. Hence, checking mono-ocular vision is very important in early disease course. This vision loss is mostly painless hence often missed initially by patient as well as clinician.
2. Spinal cord involvement: Children can present with quadriparesis / paraperesis depending on level of lesion. They can have bowel - bladder disturbances, sensory symptoms in form of acute paresthesias and sensory band and paroxysmal tonic spasms.
3. Area postrema involvement (medulla): Intractable hiccups, nausea and vomiting.
4. Acute brainstem syndrome
5. Acute diencephalic syndrome
6. Symptomatic cerebral syndrome

The diagnostic criteria of NMOSD are given in (Box 3).

Investigations

1. Neuroimaging characteristics of NMOSD[16]

A. Spinal cord MRI, acute (Fig.7)

a. Increased signal on sagital T2W extending over 3 or more vertebral segments
b. Central cord predominance (more than 70% of the lesion residing within the central gray matter)

Box 3. NMOSD diagnostic criteria[16]

Diagnostic criteria for NMOSD with positive AQP4-IgG

1. At least 1 core clinical characteristic*

2. Positive test for AQP4-IgG using best available detection method

3. Exclusion of alternative diagnosis

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:

a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome

b. Dissemination in space (2 or more different core clinical characteristics)

c. Fulfillment of additional MRI requirements, as applicable

2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable

3. Exclusion of alternative diagnosis

***Core clinical characteristics:** 1. Optic neuritis, 2. Acute myelitis, 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting, 4. Acute brainstem syndrome, 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions and 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

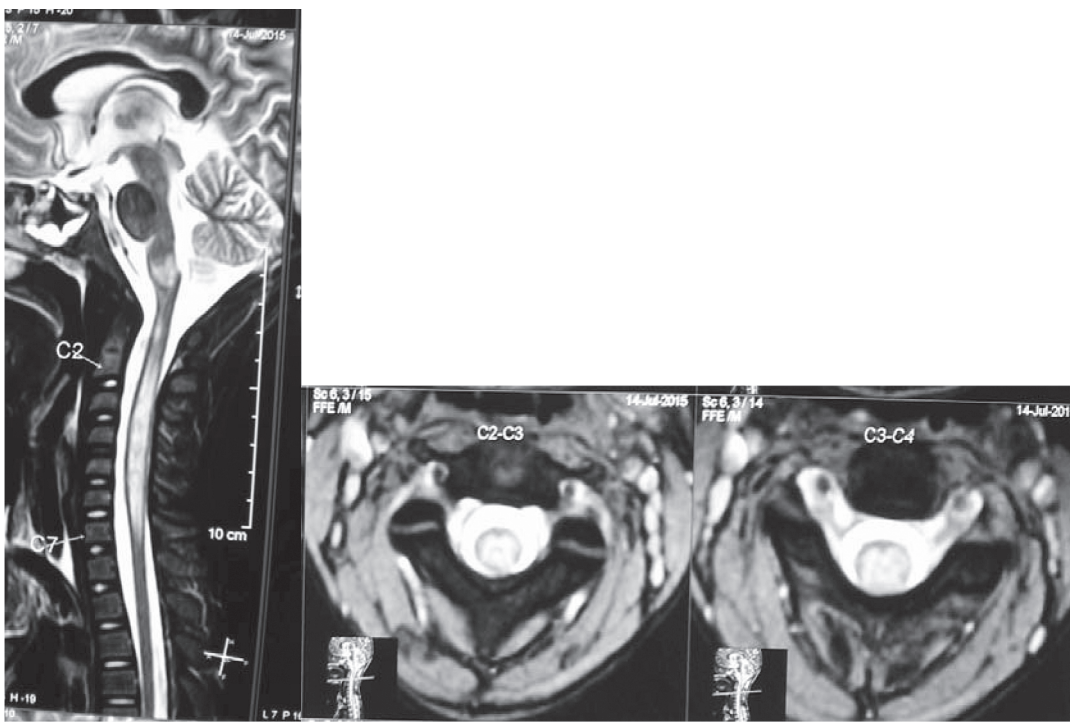

Fig.7. T2W sagittal(a) image of spinal cord showing signal changes over > 3 spinal segments along with involvement of medulla and axial(b) section showing central cord predominant lesion- NMO

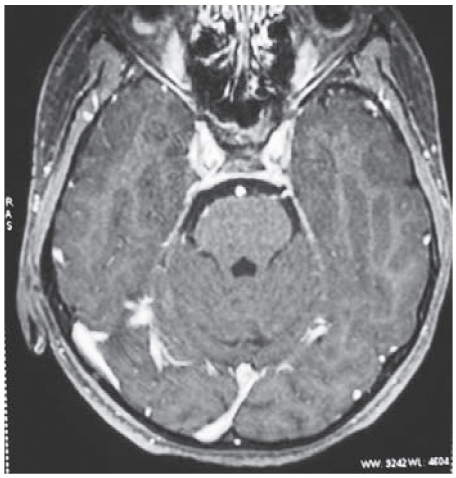

Fig.8. Optic Neuritis/NMO spectrum – post-contrast axial images demonstrating contrast enhancement of optic nerves

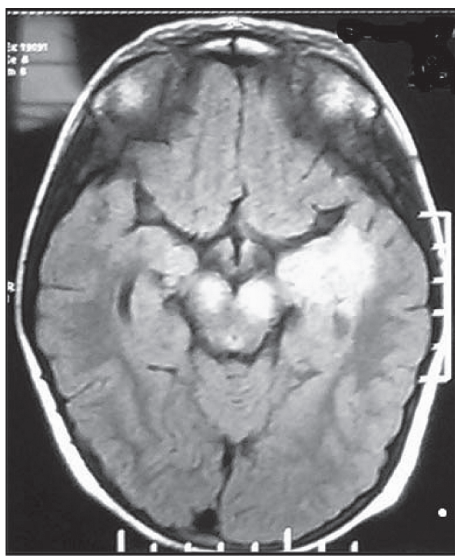

Fig.9. NMO Axial FLAIR image showing signal change in periaqueductal grey matter, cerebral peduncle and white matter around left temporal horn of lateral ventricle.

c. Gadolinium enhancement of the lesion on T1-weighted sequences

d. Other characteristic features that may be detected

- Rostral extension of the lesion into the brainstem
- Cord expansion/swelling
- Decreased signal on T1W sequences corresponding to increased T2W signal

B. Spinal cord MRI, chronic

a. Longitudinally extensive cord atrophy (sharply demarcated atrophy extending over 3 complete, contiguous vertebral segments and caudal to a particular segment of the spinal cord), with or without focal or diffuse T2 signal change involving the atrophic segment.

C. Optic nerve MRI (Fig. 8)

a. Unilateral or bilateral increased T2 signal or T1 gadolinium enhancement within optic nerve or optic chiasm; relatively long lesions (e.g., those extending more than half the distance from orbit to chiasm) and those involving the posterior aspects of the optic nerves or the chiasma.

D. Cerebral MRI: (Fig. 9)

a. Lesions involving the dorsal medulla (especially the area postrema), either small and localized, often bilateral, or contiguous with an upper cervical spinal cord lesion

b. Peri-ependymal surfaces of the fourth ventricle in brainstem/cerebellum

c. Lesions involving the hypothalamus, thalamus, or periependymal surfaces of the third ventricle

d. Large, confluent, unilateral, or bilateral subcortical or deep white matter lesions

e. Long (1/2 of the length of the corpus callosum or greater), diffuse, heterogeneous, or edematous corpus callosum lesions

f. Long corticospinal tract lesions, unilateral or bilateral, contiguously involving internal capsule and cerebral peduncle

g. Extensive periependymal brain lesions, often with gadolinium enhancement

1. Serologic testing for anti-NMO Antibody (AQP-4 Ab)[16]

Increased serum titers of aquaporin antibody, has more sensitivity than CSF antibody testing though both can be performed and specificity of assay is almost 100% at high titers. Low titers should be interpreted cautiously with clinical and radiological findings. Sensitivity ranges up to 50-60 %. Some patients may be seronegative for AQP-4 antibody but clinico-radiologically similar to NMOSD, are considered still under NMOSD. Newer research suggests that these patients may be positive for anti MOG Ab (myelin oligodendrocyte glycoprotein). Occasionally initial negative result may be positive after repeat testing during course of disease. Hence repeating test at next relapse if there is strong suspicion of NMOSD is recommended.

Cases of clinical NMO in which AQP4-IgG was detected in CSF, but not serum, have been reported but rare. Routine CSF testing of AQP4-IgG-seronegative patients is not recommended but might be considered in selected seronegative cases.

2. CSF analysis

a) CSF pleocytosis >50 leukocytes/mL, b) Presence of neutrophils or eosinophils (either >5/mL) are particularly useful in distinguishing NMOSD from MS and c) CSF glial fibrillary acidic protein may be elevated in initial few days to weeks during acute stage

Treatment[9,16,17]

The course of NMO is characterized by a high relapse rate with accumulation of neurologic disability, potentially causing permanent blindness and paralysis. Therefore, relapse prevention is crucial. Optimal therapeutic regimen has not been established.

Acute NMO attacks: Treated with corticosteroids, plasma exchange and IVIG

Relapse prevention: Azathioprine, methotrexate, mycophenolate mofetil, rituximab, mitoxantrone, cyclophosphamide, and tocilizumab

It is important to differentiate NMO from MS as commonly used drugs like interferon and natalizumab will worsen NMO attack.

Prognosis

a. Risk of relapse is high in AQP4-IgG-seropositive cases (e.g., about 60% within 1 year after LETM). Seropositivity rate between monophasic NMO and polyphasic NMO was found to be 12.5% Vs 78% in one study.

b. Clinical diagnoses of SLE, SS, or myasthenia gravis may coexist with NMOSD clinical syndromes in AQP4-IgG-seropositive patients and, in fact, their presence strengthens the diagnosis of NMOSD diagnosis.

Clinically isolated syndrome[4]

It is acute demyelinating syndrome not meeting criteria for ADEM as well as MS and may be forme fruste lesion of future MS. It is defined with following criteria.

(i) A monofocal or polyfocal clinical neurological event with presumed inflammatory demyelinating cause

(ii) Absence of encephalopathy

(iii) Absence of previous clinical history of CNS demyelinating disease

(iv) Other etiologies have been excluded.

(v) The most recent 2010 revised McDonald criteria for MS on a baseline MRI are not met.

Future trends

Researchers hope to identify an autoantigen specific for children with a monophasic, and thus a more ADEM-like presentation, to distinguish this from a chronic recurrent MS-like disease. One of the promising autoantibodies is directed against myelin oligodendrocyte glycoprotein (MOG). MOG-antibodies are strongly skewed towards children with demyelinating illness that present with an ADEM-like disease-onset. The presence of such antibodies points against a future diagnosis of MS.

Other potential candidates in MS include autoantibodies targeting myelin peptides or the potassium channel KIR4.1. Another antibody recently described is anti D2R antibody (dopamine 2 receptor) which is described in encephalitis with basal ganglia demyelinating disorders.

Points to Remember

- ***ADEM is associated with significant involvement of deep grey matter.***
- ***Periaqueductal involvement in presence of myelitis or ADEM like picture points towards diagnoses of NMO spectrum disorder.***
- ***Second line immunomodulation are increasingly playing a major role in reducing the disability in these demyelinating disorder.***
- ***Bilateral optic neuritis is a common association with ADEM whereas unilateral optic neuritis is common as first clinical event of multiple sclerosis.***
- ***Multiple sclerosis generally presents as relapsing remitting demyelinating illness.***

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BOOK REVIEW

Name : Protocols in Neonatology

Editors-in-Chief : Rhishikesh Thakre and Srinivas Murki

Publisher : Jaypee Brothers Medical Publishers (P) Ltd

Review: It is a tremendous challenge to stay updated with the many advances in neonatal care and translate them into clinical practice. This concise but comprehensive compilation brought out by the Neonatology chapter of the Indian academy of Pediatrics enables you do just that. The editors, Dr.Rishikesh Thakre and Dr.Srinivas Murki have done a commendable job. Updated and concise, yet simple and applicable in the Indian context, these evidence based protocols have been reviewed by an exhaustive panel of expert neonatologists from across the country. The book has been divided into theme based sections including care of sick newborn, well newborn, preterm / LBW / high risk newborn, neonatal dilemmas, specific therapies and miscellaneous topics. With a foreword by Dr.Ashok Deorari and Dr.Pramod Jog, the manual has an appealing and easy to read format, well laid out tables and flow charts and is a ready reckoner for neonatal fellows, resident doctors and practicing pediatricians alike. Indeed, a must have manual for any NICU.

PEDIATRIC NEUROLOGY

APPROACH TO MUSCLE DISORDERS IN CHILDHOOD

Viswanathan V

Abstract: *Muscle disorders form a major bulk of cases in any pediatric neurology clinic. It can be quite a daunting task at times to decide on the nature of the muscle disease as there are so many types and the clinical variability is huge. A unique nature of muscle disorders is that they show wide phenotypic variability even in children with the same disease. Two children in the same age group with similar genetic abnormality but showing wide variability in the phenotypic expression of the disease is not uncommon in clinical practice which makes counseling of the family members a difficult task.*

Keywords: *Muscle disorders, Children, Clinical variability, Genetics, Phenotypic expressions, Counseling.*

Due to a plethora of muscle disorders it is difficult for a pediatrician to formulate the investigations and diagnosis in a given child with suspected muscle disease. The diagnosis becomes important from the point of prognosticating and counseling the family. Some of the important points in the history and examination have been highlighted in this article.

Evaluation of a child with suspected muscle disease

History: The important aspects to be checked in history are given in Box 1.

Box 1. History in suspected muscle disorders.

1. Age of onset of the problems
2. Presenting symptoms - Head lag, delay in sitting/ standing or abnormal gait patterns, respiratory infection, scoliosis, difficulty in climbing stairs, difficulty in getting up from squatting position, ptosis, slow in writing at school
3. Courses of illness - static, improving or worsening
4. Speech, language, understanding, vision and hearing
5. Frequent breathlessness or fainting
6. Sleep pattern - Sleep pattern at night and any disturbed pattern of sleep
7. Any headache in the mornings- Usually a sign of severe nocturnal hypoventilation associated hypercapnia
8. Episodes of vomiting in the mornings
9. Drowsiness during the day time
10. Ability to carry on with usual activities of daily living like brushing, going to toilet, eating etc, on his own or requiring help for these
11. Family history of premature balding, persons becoming wheel chair bound early in life, early cataracts
12. Consanguineous marriage
13. Previous sibling deaths or repeated abortions, decreased fetal movements, poly-hydramnios, maternal drug intake particularly thyroxine, steroids, etc.
14. Condition of the baby soon after birth including APGAR score, need for resuscitation, oxygen therapy, ventilation

Common muscle disorders in infants and their characteristics

Floppy infant: Such an infant is usually very alert. It is necessary to look for facial dysmorphism (Down syndrome, Prader-Willi syndrome, Zellweger syndrome) or myopathic facies (open mouth, tented upper lips, sad looking expressionless face, loss of nasolabial folds, ptosis - bilateral/unilateral). Characteristics such as eye movements (normal or abnormal), tongue fasciculation (seen in SMA particularly) and posture (if it is frog-like) and whether spontaneous activity/movements against gravity is poor particularly in proximal muscles, have to be looked for. Chest wall movements and breathing pattern (thoraco-

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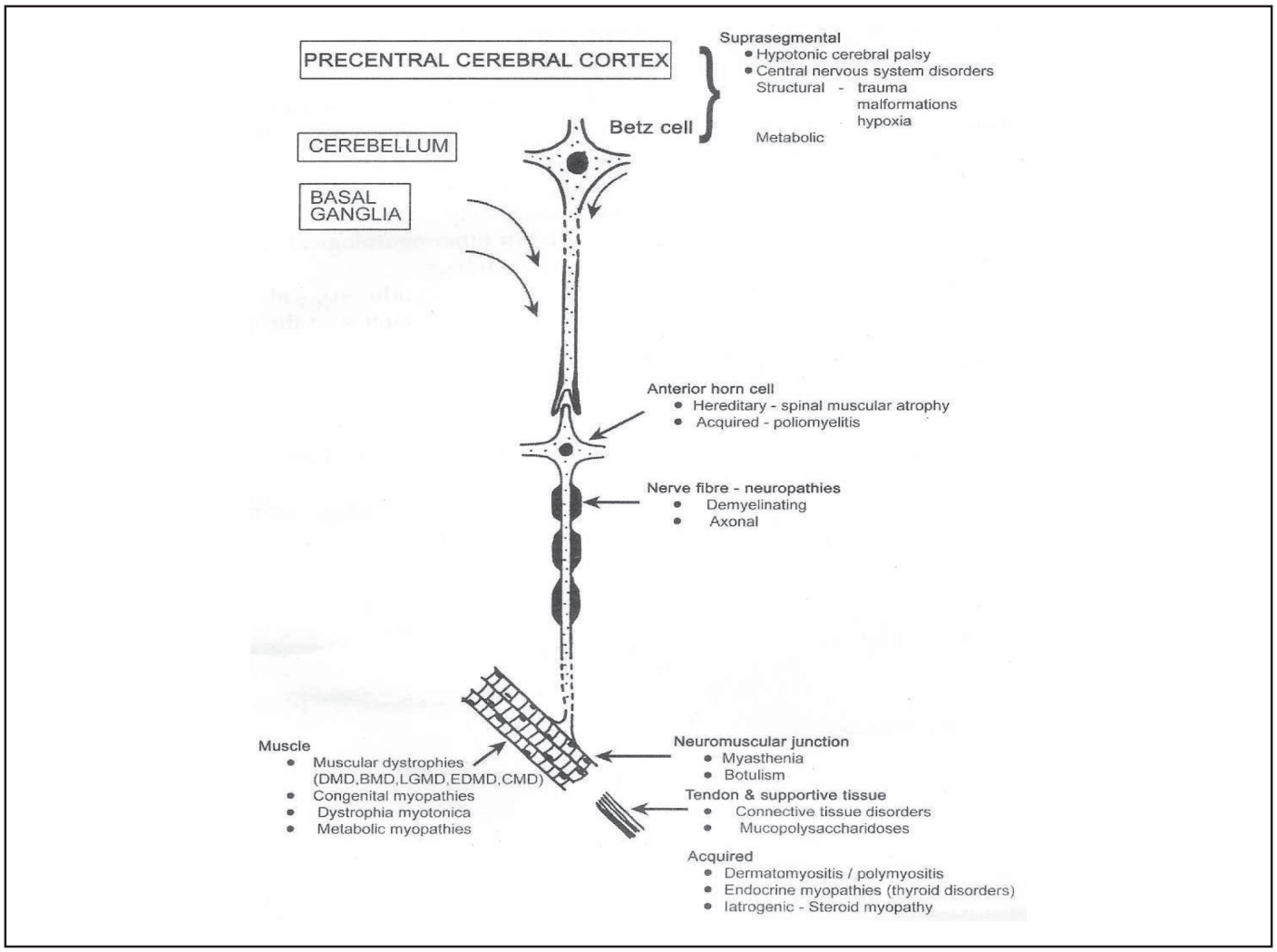

Fig.1. Schematic approach to site of lesion

DMD-Duchenne muscular dystrophy, BMD-Becker muscular dystrophy, LGMD-Limb girdle muscular dystrophy, EDMD-Emery-Dreifuss muscular dystrophy, CMD-Congenital muscular dystrophy

Picture courtesy : Veena Kalra, Practical pediatric Neurology. Arya Pulications, New Delhi, 2nd edn, 2002;p209.

abdominal or abdomino thoracic) along with chest expansion - whether it is normal or poor, shape of chest (bell-shaped chest in SMA) and testing of tone by pulling-to-sit test should be observed. Marked head lag and hypotonia may be seen on ventral suspension and deep tendon reflexes may be present, diminished or even absent. Examination of the spine, head circumference and sensory testing wherever possible would be important in these children.

All other system examination has to be done such as hepatomegaly in Zellweger syndrome and cardiomegaly for children with Down syndrome and Pompe disease. Since these children have poor or weak cough, respiratory system examination for associated respiratory illnesses has to be done. Prader-Willi syndrome may have microphallus. Common and rare causes of floppy infant are given in Table I. An approach to the site of lesion is shown in (Fig.1).

Floppy infant - common causes

Down syndrome: Hypotonia is profound and many of these children have delayed independent ambulation till about 2 years of age. Other important problems that can occur in these children are hypothyroidism, cataracts, intestinal atresias and recurrent respiratory tract infections.[1]

Hypothyroidism: In its congenital form it presents with protruding tongue, pot belly, coarse facial features, wide open anterior fontanelle, hypotonia and early developmental delay. There may be prolonged

Table I. Causes of floppy infant

Common	Rare
Down syndrome Hypothyroid SMA (Type I) Werdnig-Hoffmann disease SMA (Type II) SMA (Type III) CMD – Merosin negative – Fukuyama Walker-Warburg syndrome Muscle-eye-brain disease Congenital myopathy	Peroxisomal disorders Prader-Willi syndrome Transient neonatal myasthenia Neonatal myotonic dystrophy Pompe disease

physiological jaundice in some. Early detection of the problem and treatment with levothyroxine will prevent most of these complications and reverse the hypotonia.

Spinal muscular atrophy (SMA)

Werdnig-Hoffmann disease - Type 1: In 1991 the international SMA consortium subdivided SMA in to three types I, II and III. Spinal muscular atrophy type I, type II and type III were mapped to chromosome 5q11.2 - q13.3 locus indicating that they are allelic disorders.[2] Spinal muscular atrophy type 1 was found to be the commonest cause of floppy infants in a study done on 35 floppy infants from NIMHANS in Bangalore[3] in India. The onset is early either in utero or within the first few weeks of life. Some children appear to be completely normal for a few weeks/months before the onset of weakness. The main clinical characteristics in these children are the profound generalized hypotonia (Fig.2), frog-like posture of the limbs with lower limbs more affected than the upper limbs and proximal muscles more involved than distal, absent deep tendon reflexes, funnel-shaped chest, poor chest expansion, alert baby and in some fasciculations of the tongue. Bulbar weakness with difficulty in sucking and swallowing are seen in others. Contractures are not a feature of severe spinal muscular atrophy. These infants are prone for recurrent respiratory infections and rarely survive beyond the first two years of life.

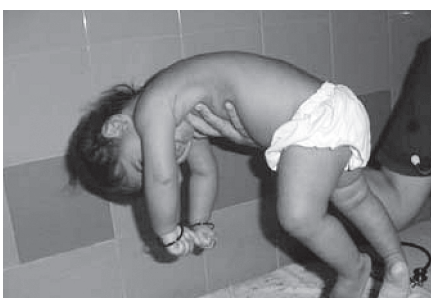

Fig.2. Marked Hypotonia

Spinal muscular atrophy - Type II: These children appear to have normal development over the first few months of life and attain sitting although with some difficulty and with increased curvature of the back. They do not walk and develop progressive contractures of the joints with severe kyphoscoliosis resulting in respiratory complication and die by early adulthood.

Spinal muscular atrophy - Type III: These children have onset of disease any time between infancy and early childhood and present with difficulty in rising from the floor, waddling gait and some coarse tremors of hands and are often confused with muscular dystrophy.

Congenital muscular dystrophy

This disease manifests soon after birth or within the first few months of life. These children also present with severe hypotonia and poor spontaneous movements.[5] They have joint contractures affecting the elbows, hips, knees, ankles and in some cases, rigid spine. Most of these children develop progressive weakness, joint contractures and respiratory compromise. The creatine phosphokinase (CPK) is elevated 3 to 10 fold. Many of them are associated with CNS involvement and other associated cerebral malformations /white matter changes.

Merosin negative congenital muscular dystrophy: This is the most common form of congenital muscular dystrophy showing complete lack of merosin on immunohisto chemistry (Fig.3). These children usually present with hypotonia and motor developmental delay. They have normal vision and hearing. Proximal muscle weakness in the legs and arms with toe walking are seen early. Tightness of the tendo-achilles with contractures may be seen. White matter changes (Fig. 4) are seen on MRI brain in the peri-ventricular areas mainly near the occipital horns of lateral ventricles, invariably after the age of 6 months in these children.[6] Thirty percent of these children

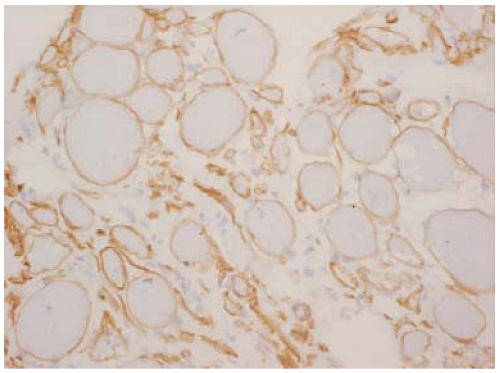

Fig.3. Merosin negative

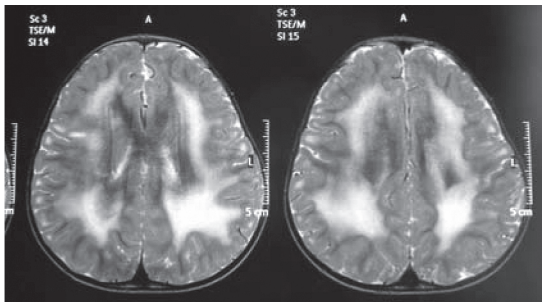

Fig.4. White matter changes on MRI brain scan

develop seizures. The genetic abnormality for this condition is described in chromosome 6q22-23.Death may occur around 10-30 years due to respiratory failure.

Fukuyama congenital muscular dystrophy

The diagnosis of Fukuyama congenital muscular dystrophy is considered when there is early infantile onset of hypotonia and weakness with contractures at the hips, knees and inter-phalangeal joints, severe delay in motor, speech and intellectual abilities in spite of relative preservation of socialization, myopathic facies, seizures and ophthalmic issues including visual impairment and retinal abnormalities.[7] Most of these children die before 10 years of age. Molecular genetic testing is available for this condition.

Walker-Warburg syndrome and Muscle-eye-brain disease: These are a similar group of conditions associated with cerebral and muscle abnormalities but much more involvement of the eyes such as with glaucoma, progressive myopia, juvenile cataracts, retinal dysplasias etc.

Congenital myopathy

There are various types of congenital myopathies described depending on the structural abnormalities of the muscle fibres visible after staining with histo-chemical methods and electron microscopy. The well known types are central core disease, mini-core disease, nemaline myopathy, myotubular myopathy, congential muscle fibre type disproportion and other non-specific myopathies. It is difficult to distinguish the various types of congenital myopathies, clinically, since majority may present as floppy infant at birth or in early infancy though some may present later in childhood. The usual clinical features are hypotonia, weakness, poor spontaneous activity and early motor developmental delay. It would be important to check the CPK levels in these children who are floppy as some of the congenital muscular dystrophies may also present as floppy infants. All other routine investigations are normal in these children.

Floppy infant – rare causes

Peroxisomal disorders

Zellweger syndrome (cerebro-hepato-renal syndrome): Facial dysmorphism including high forehead, wide open fontanelle and sutures, shallow orbital ridges, low nasal bridge, micrognathia and external ear deformity are seen. Neurological manifestations are dominated by severe hypotonia, depressed or absent tendon reflexes and poor sucking and swallowing.

Prader-Willi syndrome: This condition is characterized by profound hypotonia in the neonatal period, feeding swallowing problems and dysmorphism. The striking features are the hyperphagia and obesity that develop by the second year of life. Other features are hypogenitalism, cryptorchidism, mental retardation and short stature.[8] The syndrome is associated with an interstitial deletion of chromosome 15q 11-13 of paternal origin.[9]

Transient neonatal myasthenia: This condition is due to transfer of antibodies directed against acetyl choline (Ach) receptor from the maternal to fetal circulation.[10] About 10% to 15% of the infants born to myasthenic mothers are affected. Symptoms can occur soon after birth to about 3 days after birth. Hypotonia, facial weakness, poor cry, impaired swallowing and even respiratory distress occur in some requiring ventilation. Most of these children improve within a few days to weeks after birth.

Neonatal myotonic dystrophy: Hypotonia, facial diplegia, respiratory insufficiency, arthrogryposis are common and

often they are small for gestational age. The condition is inherited from the mother. Myotonia is rarely observed during infancy and the infant usually dies within the first few weeks after birth.

Pompe disease (Fig. 5): This is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha glucosidase (GAA).[11] There is a steady accumulation of glycogen in target tissues resulting in organ failure or death. The defective gene site is chromosome 17q 25.2-25.3. Three distinct clinical forms are recognized: infantile, childhood and adult. Marked hypotonia and congestive heart failure are the initial symptoms. Muscle weakness with severe respiratory distress is seen in these infants. The recent development of recombinant alpha-glucosidase has dramatically improved the life expectancy and quality of life of infantile-onset disease with improvements in respiratory and motor function observed in juvenile or adult-onset cases.[12]

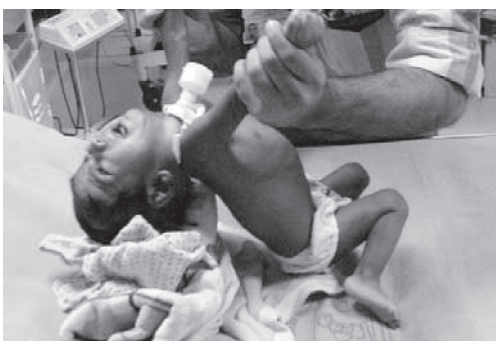

Fig.5. Infant with Pompe disease with tracheostomy

Common muscle disorders in older children and their characteristics

Duchenne muscular dystrophy

Onset is in early childhood. Toe walking and difficulty in climbing stairs and rising from the floor are early symptoms. Gower's sign is seen due to pelvic girdle muscle weakness and becomes apparent by about 6 to 7 years of age. Lumbar lordosis and waddling gait appear later. Calf hypertrophy and less frequently hypertrophy of vastus lateralis and deltoids may be seen. Many of these children become wheel-chair-bound by 12 years. Scoliosis and respiratory difficulties occur usually at this stage. Cardiac involvement is seen towards the later stages. Approximately 20% to 30 % have subnormal range of intelligence quotient. The diagnosis is made based on very high creatine phosphokinase, myogenic pattern on EMG, lack of dystrophin seen on immune-cytochemistry of the muscle biopsy.[13] Genetic testing is performed looking for deletions/ translocations in the DMD gene located in the short arm of X chromosome in the band Xp21. Prenatal diagnosis and carrier testing are possible.

Becker muscular dystrophy

This condition is allelic to Duchenne muscular dystrophy with onset after 5 years up to adolescence. Patients continue to walk well into adulthood. Pseudohypertrophy of calf muscles, pes cavus and Achilles tendon contractures with absent ankle jerks may occur. Dystrophin staining shows about 10% – 40% positive fibres.[14] Creatine phosphokinase is elevated. Many of these patients experience calf pain and muscle cramps after exercise.

Limb girdle muscular dystrophies

This is a group of clinically and genetically heterogenous type of muscular dystrophy characterized by weakness and wasting at the shoulder and pelvic girdle. The age of presentation and the severity are also widely variable.

Sarcoglycanopathies: Sarcoglycanopathies are a group of autosomal recessive muscular dystrophies designated as α, β, γ, or δ sarcoglycanopathy. Most of these children present in the first decade with onset before 5 years of age. This disorder can affect both boys and girls since it is autosomal recessive. Sarcoglycanopathy should be particularly suspected in a child born to consanguineous parents presenting with proximal muscle weakness and calf muscle hypertrophy, elevated CPK level and myopathic pattern on EMG.[15] The progression of this disease is similar to DMD but not so severe and rapid and so many of these children tend to remain ambulant longer.

Myotonia congenita

This condition is rare in children with stiffness of the muscles and presents early in life. Myotonic dystrophy is more common in adults.

Myasthenia

Myasthenia is characterized by abnormal fatigue after sustained muscle activity and by improvement after rest. There are three main clinical varieties that occur during childhood.

1. Transient neonatal myasthenia in the infant born to a mother suffering from myasthenia (discussed earlier)
2. Congenital or infantile myasthenia
3. Juvenile myasthenia which is similar to the adult variety.

The characteristic feature of myasthenia is the variability of the weakness – the child appears normal on awakening but fatigue and weakness appear following exercise and are more marked towards the end of the day.

Congenital myasthenia: Children usually present with fatigable weakness of skeletal muscle (e.g; ocular, bulbar, limb muscles) with onset at birth or early childhood. Cardiac and smooth muscles are not involved.[16] These children may get in to sudden episodes of respiratory insufficiency precipitated by fever, infections and excitement. In the neonatal onset type feeding difficulties, poor suck, cry, eyelid ptosis, facial and generalized weakness may be seen with poor response to medications.

Juvenile myasthenia: Often this is insidious in onset with ptosis with or without ophthalmoplegia. The course tends to be slowly progressive with marked fluctuations. In general most of these patients tend to be better soon after waking or a period of rest and tend to tire/show more symptoms towards the end of the day.

Mitochondrial myopathies

These are a group of disorders characterized by muscle weakness and abnormal muscle histology. Kearns-Sayre syndrome shows external ophthalmoplegia, retinal degeneration, cardiac conduction defects and sometimes diabetes, deafness and ataxia. Chronic progressive external ophthalmoplegia, MELAS (Mitochondrial encephalo-myopathy, lactic acidosis and stroke like episodes), MERRF (Myoclonic epilepsy and ragged red fibre disease) are other mitochondrial disorders which have been well described. In general one should consider mitochondrial disorders in a child presenting with multisystem involvement.

Examination of an older child with suspected muscle/neuro-muscular disorder.

The common clinical findings are given in Table II.

Investigations in a child with suspected muscle disease

(i) CPK: High in muscular dystrophies but normal in myopathy

(ii) EMG: Fasciculations, denervation potentials and high amplitude polyphasic motor potentials in anterior horn cell disorders (SMA) and small amplitude polyphasic motor units in myopathy/muscular dystrophy.

(iii) Nerve conduction velocity: Normal in anterior horn cell disorders and myopathy but decremental response to repetitive nerve stimulation seen in myasthenia.

Muscle Biposy: Particularly of value in differentiating the various types of myopathy and muscular dystrophies. In general routine histology and immuno-histochemistry is useful when one suspects muscular dystrophy (high CPK) while routine histology and electron microscopy is useful when one suspects congenital myopathy or mitochondrial disorder (normal CPK). A schematic approach to a child with suspected muscle disease is given in Fig.6.

Table II. Muscle/Neuro-muscular disorders - Clinical findings

Head / Face	Gait and Posture	Muscle characteristics
Hydrocephalus - Walker-Warburg Syndrome	Gait – Wide based gait - in most myopathies	Proximal muscle weakness –Most muscular dystrophies and myopathies
Facial dysmorphism- Down, Prader- willi	Toe walking - DMD Walking with feet externally rotated/ Talipes valgus - common in myopathies.	Calf muscles – Hypertrophy in DMD
Facial weakness - Congenital myopathy	Scoliosis – Postural / permanent - SMA – Type 2, DMD, congenital myopathies, congenital muscular dystrophies	Calf muscles - thinning Charcot Marie tooth disease.
Ptosis +/- ophthalmoplegia - myasthenia, mitochondrial disorders	Arthrogryposis – congenital muscular dystrophies	Depressed or absent tendon jerks – may be feature of all the myopathies / muscular dystrophies / SMA
Big tongue – DMD		
Fibrillations in tongue - SMA		

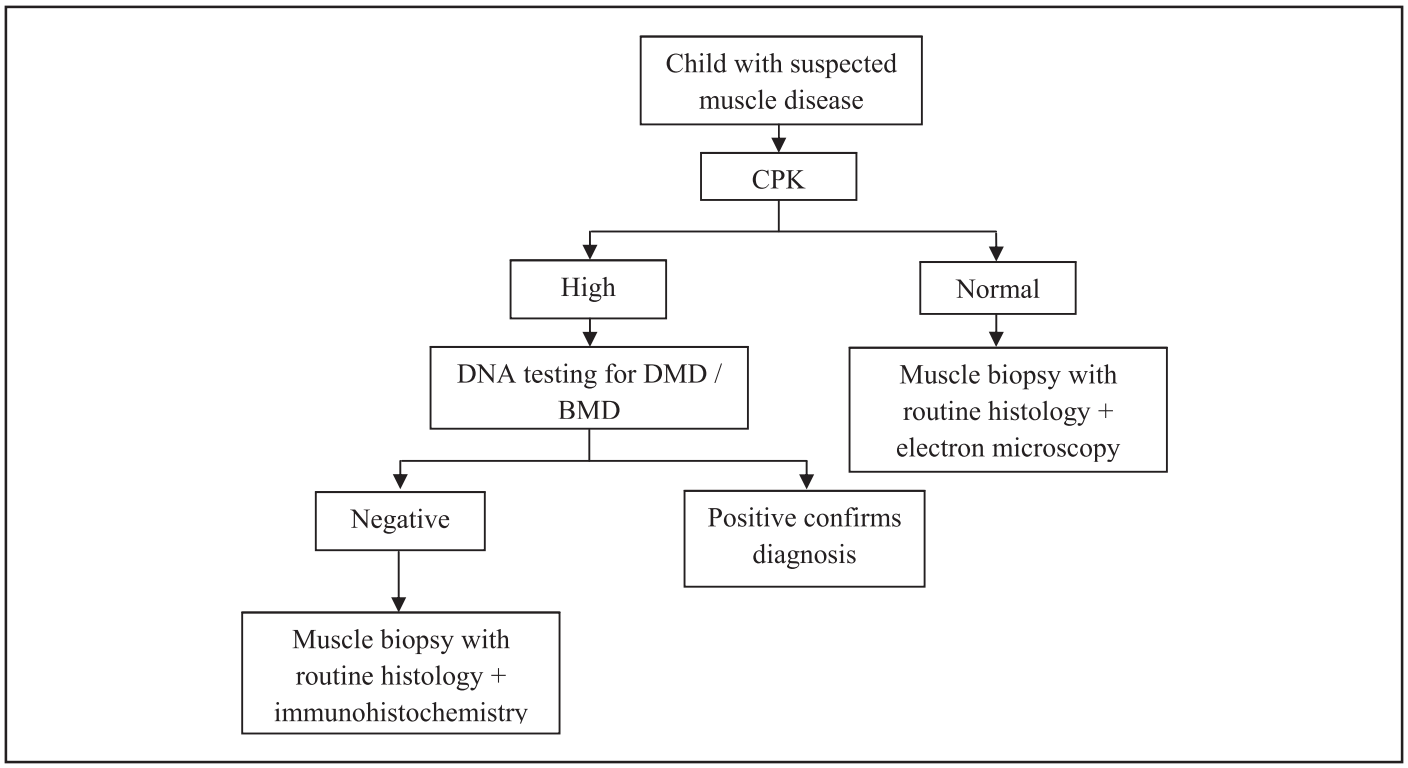

Fig.6. Schematic approach to a child with suspected muscle disease

Management

Treatment of Juvenile myasthenia is mainly symptomatic with partial amelioration in some with anti-acteylcholinesterase medication. Thymectomy and immuno-modulatory agents are rarely beneficial in these children. Drugs like chloroquine, ciprofloxacin, procaine, lithium, phenytoin, beta blockers, procainamide and quinidine are known to affect neuromuscular transmission and exacerbate symptoms of myasthenia and should be avoided.

Management of children with other muscle disorders is supportive as most of these disorders have no cure as yet although there is lot of ongoing research. Supportive management includes correct diagnosis and counselling regarding the likely prognosis, carrier testing and prenatal diagnosis for the next pregnancy have a role. These children require close follow up by a team of experts mainly directed by neurologists with guidance and support from cardiac, pulmonary, orthopaedic, nutrition and rehabilitation experts. The rehabilitation should include care in terms of appropriate orthotics, supportive care at home including wheel chairs, bed, toilet facilities, etc. It is important that doctors discuss with the families regarding the plans for end of life care towards the later stages of the disease and prepare the families for what to do in the event of a need for ventilation/ICU care. This is very important as otherwise it becomes a very difficult time for everyone concerned during an emergency.

Points to Remember

- ***It is important to make a correct diagnosis of muscle disorders and plan the investigation of choice accordingly.***
- ***Genetic diagnosis is helpful in many cases, not only to prognosticate but also to test for carrier status and counsel regarding the chance of recurrence.***
- ***Early intervention including physiotherapy, care of respiratory and cardiac issues helps in improving the quality of life and longevity in these children.***
- ***Some of the children with muscle disorders may improve over time.***

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CLIPPINGS

Treatment with propranolol for infantile hemangiomas: Single-center experience

Infantile hemangiomas (IHs) are the most common soft tissue tumors of infancy. Although spontaneous regression is expected, medical treatment is needed in approximately 10-20% of cases. The present study was aimed to assess the safety and efficacy of systemic propranolol for the treatment of IH. Medical records of 34 eligible patients were analyzed retrospectively. Treatment indications were local complications (hemorrhage, ulceration) in 38.2% of patients, cosmetic risk and face deformity in 35.3%, life-threatening organ dysfunction in 17.6% and impending visual impairment in 8.8%. The median age at start of treatment with propranolol was 3.5 months (range, 2-65 months). The median duration of propranolol treatment was 8 months (3-12). Response was graded as excellent (>75% improvement) in 30 patients (88.2%) and good (50-75% improvement) in 3 (8.9%). Recurrence was not observed after termination of treatment. None of the patients showed severe side effects at the beginning of or during the treatment. The study concluded that propranolol is a well-tolerated, efficacious and safe drug for treatment of IH. It can be initiated and administered in the outpatient setting. It also supports the excellent effect and good tolerance of this novel therapy and recommends the use of propranolol as first line treatment in Infantile hemangioma.

Turhan AB, Ozcan Bor, Zeynep Canan Ozdemir. Treatment with propranolol for infantile hemangiomas: Single-center experience. J Cosmet Dermatol April 2016. Version of Record online: 7 APR 2016, DOI: 10.1111/jocd.12220

PEDIATRIC NEUROLOGY

HYDROCEPHALUS

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Abstract: *Pathophysiology, clinical features, management and complications of hydrocephalus have been discussed in this article. Emphasis is on practical aspects relevant to the pediatrician and residents. Procedures have been dealt with in detail wherever necessary. Endoscopic third ventriculostomy which has become safer and improvements in shunt systems are discussed.*

Keywords: *Hydrocephalus, Childhood, Shunt, CSF.*

Hydrocephalus is defined as enlargement of brain ventricles (Internal Hydrocephalus) and/or subarachnoid space (external hydrocephalus). Shunt surgery for hydrocephalus is the most common neurosurgery performed in children.[1,2]

Wernicke[1] did the first sterile ventricular puncture and external ventricular drain. Walter Dandy was among the first to perform endoscopic choroid plexectomy and endoscopic third ventriculostomy which improved our understanding of hydrocephalus. Eugene Spitz performed the first ventriculoatrial shunt with a ball valve. John Holter[1] used silicone material and a valve in a shunt tube for his son, heralding the age of improved material for shunt. Improvement in shunt hardware with introduction of antisiphon device, programmable shunt tube, flow regulated valves and antibiotics have made treatment of hydrocephalus safer. With improvement in fibre-optics and evaluation of anatomy with magnetic resonance imaging-third ventriculostomy has made a comeback as reliable alternative in selected patients with hydrocephalus.[2] Indian shunts like Ceredrain made possible reliable and cheaper shunt hardware in the late 1990's with dramatic improvements in the life of patients.

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CSF production and circulation[3,4,5,6]

Cerebrospinal fluid is produced predominantly by choroid plexus in the ventricles and to a lesser extent by ependyma lining the ventricles. It is produced at a rate of 0.35ml/minute with a daily production around 400 to 500ml. CSF volume varies from around 60ml in infants to around 150ml in adults. It is absorbed by arachnoid villi/ granulations in superior sagittal sinus as well as via spinal leptomeninges, vascular and nerve root sleeves. There is a 5-7 mm hydrostatic pressure difference between superior sagittal sinus and subarachnoid space which facilitates absorption.

Intracranial Pressure (ICP) raises from 0-3 mm Hg in preterm, 2-6 mm Hg in infants, 3-8 mm Hg in children to 10 to 15 mm Hg in adults.

CSF is produced in lateral ventricles, passes through foramen of Munro to third ventricles. From third ventricles it passes through aqueduct of Sylvius to fourth ventricle. The outlet of fourth ventricle is through foramen of Magendie and Luschka in its roof. CSF passes through subarachnoid space surrounding the cerebellum and brainstem via the tentorial incisura to enter supratentorial space. It passes around cerebral convexity to enter arachnoid villi in superior sagittal sinus (Fig.1).

Pathophysiology[3,4,5,6]

CSF overproduction

Choroid plexus tumours (papilloma and carcinoma) increase CSF production as well as CSF protein which impairs absorption resulting in hydrocephalus.

Obstruction along CSF pathway

CSF may be blocked by congenital malformation, hemorrhage, tumour and infection along its long pathway from choroid plexus in lateral ventricle to arachnoid villi in the superior sagittal sinus. These include the following possibilities:-

a) At foramen of Munro and third ventricle the block may be caused by subependymalgiant cell astrocytoma, colloid cyst, craniopharyngioma, optic

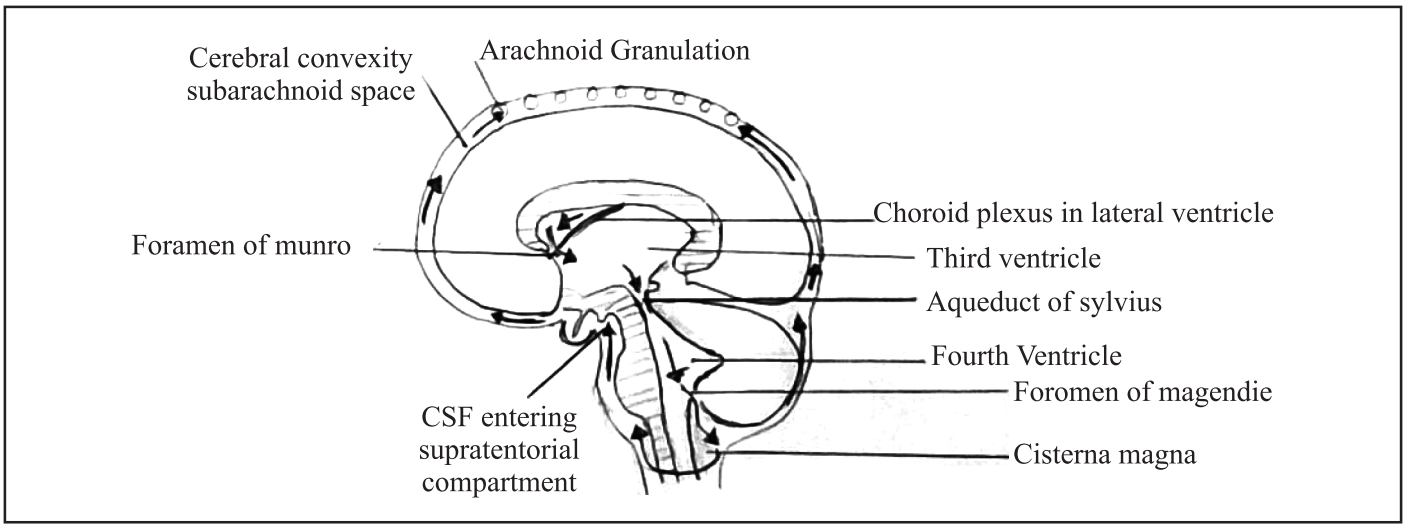

Fig.1. Normal CSF Pathway

pathway glioma, vein of Galen malformation and pineal region tumours.

b) The aqueduct of Sylvius may be blocked primarily by malformation or secondarily by intrauterine infection, other infections including tuberculosis or hemorrhage.

c) Fourth ventricle may be obstructed by congenital causes like Dandy Walker malformation, Arnold Chiari malformation Type II with myelomeningocele and tumours such as medulloblastoma, ependymoma and astrocytoma.

d) Subarachnoid space at tentorial hiatus is obstructed by extensive basal tuberculous meningitis exudate. Tuberculous as well as gram negative infections can produce extensive adhesions along CSF pathway producing multiloculated hydrocephalus.

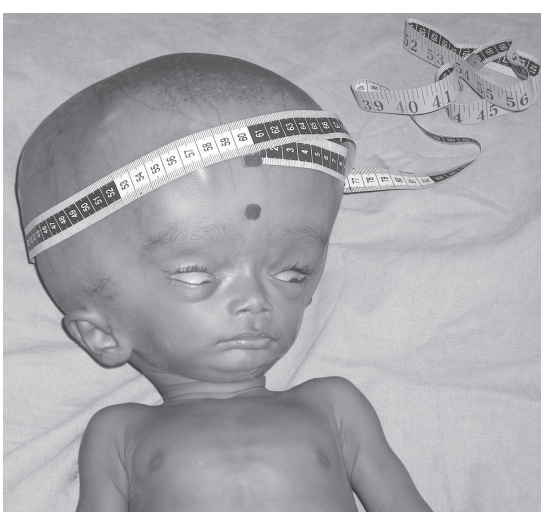

Fig.2. Infant with hydrocephalus and sunset sign

Infections and hemorrhagic by-products may be blocked by arachnoid granulation along superior sagittal sinus producing communicating hydrocephalus. Cerebral venous thrombosis, idiopathic intracranial hypertension due to venous cause, superior vena caval obstruction, platybasia may produce a similar picture.

Intraventricular hemorrhage occurs predominantly in premature infants and accounts for upto 25% of birth trauma. However, most are asymptomatic with immature brain accommodating ventriculomegaly before enlargement of head. Probability of hydrocephalus correlates with amount of blood in CSF.

Clinical presentation[3,4,5,6]

Infants

Sudden obstruction of CSF pathway may lead to rapid ventricular dilatation proximal to block along CSF pathway. Signs and symptoms may vary according to site of block, but not significantly contributory unlike chronic hydrocephalus. In premature babies and infants, rapid increase in head circumference produces tense bulging fontanelle, scalp vein distension, sun-setting sign, obtundation, vomiting, episodes of apnoea and bradycardia (Fig.2). Transillumination may be positive if thickness of cortical mantle is less than 1 cm.

Infants presenting with chronic symptoms present with irritability, drowsiness and abnormal head circumference increasing across centiles. Upward gaze palsy is usually absent in premature infants. Oculomotor abnormalities include sixth nerve and third nerve palsies. Papilledema is rare in this age. However retinal vein engorgement/ haemorrhages on fundus examination may occur.

Percussion over dilated ventricles may produce a cracked pot sound (Macewen's sign).

Children

Above two years of age children present with headache, vomiting, decrease in school performance, memory loss, behaviour problems, visual impairment/ loss, large head if hydrocephalus started before 2 years of age. On examination they may have papilledema, sixth nerve palsy, Parinaud's syndrome, optic nerve atrophy, gait disturbance and micturition disturbances. Seizures are uncommon symptom in internal hydrocephalus but may indicate external hydrocephalus (CSF around cerebral convexity). Subtle endocrine disturbances are present in children with long standing hydrocephalus. Head circumference should be regularly monitored in all children as part of well baby screening and noted on chart. Any value above two standard deviations should prompt careful evaluation. Increasing intracranial tension requires rapid treatment with simple ventricular drainage, which can be done at bedside through anterior fontanelle.

Procedure of emergency ventricular tapping in infants

The head is showed or the hair is clipped or removed using a hair removal cream. Skin is prepared with 10% iodine solution or 2% chlorhexidine solution in isopropyl alcohol for 5 minutes. Quite often, this is done in a side room or ward under local anesthesia. It is very important to hold the infant's head immobile. This should be emphasized as any movement can be catastrophic. A 23 gauge spinal needle is inserted in the right side laterally in the anterior fontanelle in midpupillary line. In case of a hugely dilated ventricle, the needle is passed under the skin (subcutaneously) anteriorly in midpupillary line for a few millimetres and then dipped under the cortex to enter the ventricle. This prevents formation of CSF fistula. Collect CSF for investigation to rule out infection and as well as let out upto 30ml to tide over impending respiratory arrest. Infants with not so large ventricles which do not reach to the surface are better tapped by neurosurgeons. It should be done with due care to overcome a crisis situation. If there is bleeding wait till CSF clears. Avoid repeated puncture and definitely not more than twice.

Imaging[3,4,5,6]

Ultrasound

Ultrasonogram (USG) of the head is the most common imaging done in newborns and infants. Advantages are, no risk of radiation injury to immature brain or lens. Serial imaging can be done to look for progression in asymptomatic or minimally symptomatic children, especially hemorrhage and hydrocephalus in premature infants. It can be used not only to visualize intrauterine hydrocephalus but also in follow-up after shunting. The disadvantages are inadequate visualisation of fourth ventricle as well as subarachnoid spaces. The image resolution is poor and is operator dependant.

Computerised tomography (CT)

CT scan is the imaging of choice before any definitive procedure or surgery which objectively measures ventricular dimensions like Evan's ratio, bifrontal ratio, size and ballooning of third ventricle, and temporal horns are objectively measured. Transependymal seepage of CSF around frontal horns and less in occipital horns in active and acute hydrocephalus can be seen. Tumour, cyst, features of infection, vascular and congenital malformations are noted. The site of obstruction in CSF pathway can be located. With contrast administration tumours, vascular malformation as well as basal exudates in tuberculous meningitis can be seen well. An apparently normal ventricular size cannot rule out hydrocephalus in children.

Magnetic resonance imaging (MRI)

MRI has the ability to give greater anatomical and, pathological details as well as CSF flow characteristics. The disadvantages include length of scanning time, claustrophobia for young and necessity to stay motionless for long periods often requiring anaesthesia in children and special equipment for monitoring. Though expensive, only MRI can show cause of aqueductal stenosis due to congenital causes like forking, septum and tuberculous granuloma. Phase contrast MRI helps in studying CSF flow and dynamics in aqueduct of Sylvius, in the fenestration in third ventriculostomy and around tonsillar herniation in Arnold Chiari malformation which helps in evaluating the results of therapy.

Treatment[2,3,4,5,6,7,8]

Medical treatment

1. IV Mannitol at 0.25 to 0.5 gm/kg/dose over 10-20 minutes till CSF aspiration/drainage is carried out to reduce ICP in an emergency.
2. Diuretic therapy in less than 1 year of age for temporary hydrocephalus/ hemorrhage in birth trauma in an non-emergency situation: (a) Tab. Acetazolamide 25mg/kg/day in 3 divided doses and

can be combined with Tab. Sodabicarbonate to avoid acidosis, (b) Tab.Furosemide 1mg/kg/day in divided doses may be added to acetazolamide to increase effectiveness,

3. Serial lumbar puncture may be effective to avoid permanent shunt in post-hemorrhagic communicating hydrocephalus with minimal symptoms.

Surgical treatment

External ventricular drainage (EVD): EVDs is usually done as an emergency to relieve acute hydrocephalus either in the operation theatre or bedside, taking full aseptic precautions. Usually done through frontal burr hole sited 1cm in front of coronal suture and 3 cms from midline on the right side. Occipital burr hole 5-6 cms above inion and 3-4 cms from midline may be used. Ventricular catheter is tunnelled subcutaneously for about 3 cm before ventricular insertion. Burr hole is made, dura is catheterised and opened. Trajectory of ventricular tapping is determined by size of ventricle. In frontal burr hole it is directed at the point of intersection of mid-sagittal line and line connecting external acoustic meatus. For occipital burr hole, it is pointed towards ipsilateral medial canthus. With ventricle tapped with brain needle, appropriate length of catheter is placed in situ. It is connected to closed drainage system. The amount of CSF drained is determined by the height drainage bag is kept from the patients ear. Usually it is kept 10 cm above ear to keep intracranial pressure around 8-10 cm of water. It is important to use strict aseptic precaution while handling EVD.

In case of hemorrhagic and infectious causes, serial cell count, sugar, protein and culture of CSF are done. If protein level falls below 0.5gram/L, trial closure of drainage may be done to check if high intracranial pressure signs and symptoms develop. In case of infection at least three consecutive cultures should be sterile before placement of permanent shunt. EVD may be used to instill antibiotics intraventricularly. If ICP does not raise on EVD closure, it may be closed or converted into a closed shunt system if ICP raises.

Surgical treatment of cause: In case of tumour/cyst obstructing CSF pathway, excision where feasible with/without temporary CSF diversion in the form of external ventricular drainage is adequate for treatment of hydrocephalus.

Endoscopic third ventriculostomy (ETV)[2]

Nearly 20% of hydrocephalus are treated by ETV. If CSF obstruction is anywhere between lateral ventricle and the site to before CSF enters cerebral convexity around tentorium, i.e., obstructive hydrocephalus, ETV is preferred. It is also the best option in infective hydrocephalus as it avoids any hardware. However only one-third of tuberculous hydrocephalus are obstructive and in rest of the cases it may be adjunct to ventriculo-peritoneal shunt. In case subdural hygroma develops after shunt insertion, ETV may be tried before flow regulated shunt. ETV can be performed as emergency procedure before tumour/cyst resection. ETV is also the procedure of choice in selected patients with slit ventricle syndrome. However in case of extensive adhesions in subarachnoid space, ETV is likely to fail. ETV is favourable even for infants with obstructive hydrocephalus. Endoscopic approach is the treatment of choice for mulitloculated hydrocephalus to break septation and convert it into as few cavities as possible which can be shunted

Shunt systems

Shunting is the most widely used form of treatment in hydrocephalus. CSF is drained from ventricles or lumbar subarachnoid space to peritoneum, right atrium or pleura. Thus they are called ventriculoperitoneal, ventriculoatrial, ventriculopleural or lumboperitoneal shunt accordingly .

Ventriculoperitoneal (VP) shunt is the most common shunt accounting for more than 90% of all shunts. Shunt system consists of ventricular catheter, valve mechanism and peritoneal catheter. It can be performed on all forms of hydrocephalus except in active infectious state.

Valves used with shunts are of two types, pressure regulated or flow regulated. Pressure valve may be a differential pressure valve or adjustable pressure valve (pressure adjusted using external magnet). Differential pressure shunt may be low, medium or high pressure opening at 5 cm, 10 cm and 15 cm of water. Medium pressure shunt is the most commonly used shunt. Adjustable pressure shunts are expensive and do not offer any major advantage routinely in all cases. Flow regulated valve maintains a constant flow irrespective of pressure. Flow regulated valves are used in infants with large ventricle with thin cortical mantle to avoid overdrainage and subsequent subdural hygroma formation. Anti-siphon valve is usually integrated along with valve mechanism to prevent excess drainage in upright position because of gravity.

Ventriculoatrial(VA) shunts are inserted through the common facial vein, internal jugular vein and placed in the right atrium using X-ray guidance in children when peritoneum in not suitable because of infection and

adhesion. They have a higher rate of septicemia compared to VP shunt, requires frequent lengthening in a growing child and pulmonary complications as well.

Ventriculopleural shunts are inserted only in children above 7 years of age because of risk of fluid overload. Pleura is a negative pressure cavity and hence the risk.

Lumboperitoneal (LP) shunts are inserted in communicating hydrocephalus, with help of Tuohy needle into the lower lumbar subarachnoid space in children above 2 years. Laminectomy is to be avoided as scoliosis risk is higher. Some manufacturers incorporate a valve in LP also to regulate drainage. There is a risk of Arnold Chiari malformation type 1 with LP shunts and hence avoided in children.

All shunts are done are under general anaesthesia under strict sterile precautions usually as first in the morning in theatre to rule out infection. Minimal staff should be present and the procedure should be done with minimal skin contact, using latex-free gloves, talc-free gloves by washing with sterile saline and by experienced operator to reduce complications.

External hydrocephalus (EH) is CSF collection over cerebral convexity, interhemispheric fissure and basal cisterns. It is usually asymptomatic, occurs in infancy and has to be distinguished from chronic subdural hematoma which presents with seizures, headache and vomiting and needs drainage. EH usually undergoes spontaneous resolution by 3 years of age only very rarely requiring shunt.

Dandy-Walker malformation with hydrocephalus might require two catheters to be placed intracranially (one in ventricle and other in posterior fossa cyst) connected via Y connector to a single chamber and peritoneal catheter.

Intrauterine surgery for hydrocephalus is done by shunting the ventricle to amniotic cavity before 24 weeks of gestation to produce the best cognitive outcomes for child.

Complications of shunt[3,4,5,6,7,9]

Immediate complications

1. Infection

Infection is high in prematurity, infants less than 6 months of age and in presence of spinal dysraphism. Infection is usually due to Staphylococcus epidermidis. Occasionally staphylococcus aureus, streptococci, gram negative bacteria, pneumococcus, H influenza or meningococcus are the causative organisms. Infection presents as redness along the shunt track, cranial or abdominal incision site with fever and raised WBC count. Tapping the reservoir for CSF evaluation and treatment with appropriate antibiotics (intravenous + intraventricular) will clear the infection in a small minority especially with pneumococcus, meningococcus and H influenzae infection.[6] The others will require shunt removal, external ventricular drain and once three consecutive CSF samples are negative on culture, reinsertion of shunt may be done. Antibiotic impregnated[10] shunts have shown decreased rate of shunt infection in some studies and may be advised where feasible, though costly.

2. Malfunction effects

a) Immediate - Child presents with signs of raised intracranial pressure as before surgery. Wrong placement of shunt tube in preperitoneal fat, migration of ventricular tip to temporal horn, disconnection, impaction with choroid plexus, blood clot peritoneal adhesion/cyst and valve dysfunction are the causes. Proper placement of the shunt should be done under aseptic precautions. Connection in shunt assembly needs to be secured with non-absorbable sutures. Ventricular end impaction can be flushed via reservoir for relief while occluding the peritoneal side of reservoir, otherwise revision of ventricular end and placement of ventricular end in frontal horn which is devoid of choroid plexus gives good results. Peritoneal end block can be released by flushing the reservoir into peritoneal side while occluding the ventricular side. If it fails re-insertion into a fresh site in peritoneum may be needed with culture taken to rule out infection. Valve dysfunction needs shunt revision fully.

b) Delayed - Shunt dysfunction can happen after a few months or years due to same reasons mentioned above in indolent form. Diagnosis is important to localize the site of malfunction shunt-O-gram needs to be done. Two types of shunt-O-Gram: Radio nucleotide and X-ray fluoroscopy are done. X-ray shunt O gram: the skin over shunt reservoir area is prepared and disinfected with iodine/chlorhexidine solution. The reservoir is tapped with 25 gauge butterfly needle. CSF is collected for cell count, glucose, protein, gram stain and culture. 3 to 5 ml of non-ionic (low concentration) contrast which is diluted with water to 10ml is injected into the reservoir while occluding

the distal flow in the peritoneum. Abdomen is scanned using fluoroscopy to look for contrast in abdomen. Cranium is imaged to verify flow into the ventricle. Normally spontaneous flow of contrast should be seen in abdomen in ten minutes. Otherwise patient is make to sit up and if necessary shunt reservoir is pumped. Diffusion of contrast into abdomen is looked for and it should not localize as in pseudocyst. The cause of dysfunction is treated as described above.

3. Bowel perforation: This can happen immediately or later. Shunt is externalised, infection treated and shunt is reinserted.
4. Hemiparesis: It can be due to inadvertent injury to motor cortex during ventricular catheter passage during insertion. This usually improves within a few days.
5. Intracranial hemorrhage: Hemorrhage occurs due to choroid plexus injury during insertion. Coagulopathy is has be ruled out. Surgeon usually waits for bleeding to clear/or converts it into external ventricular drainage.
6. Peritubal CSF leak: This happens because of puncture of tube by suturing needle during insertion and needs revision of shunt.
7. Wound dehiscence: For wound dehiscence antistaphylococcal antibiotics like cefuroxime, cloxacillin, clindamycin, linezolid or vancomycin with aminoglycosides can be started after taking wound swab for culture. Daily dressing is required to see if it heals with appropriate antibiotics. Shunt removal and revision in another site is required in case of infection.
8. Slit ventricle syndrome:[9] Presents as intermittent transient symptoms of shunt dysfunction usually as headache lasting for 10 to 90 minutes. On CT small ventricles are seen. Most commonly present between 5 to 10 years of age in children who have been shunted in infancy. This has to be differentiated from migraine as well as venous hypertension causing decreased CSF absorption with distended cortical subarachnoid space and overdrainage which produces headache on upright posture and relieved by lying down. Over drainage is treated by upregulation of valve pressure. Slit ventricle syndrome is treated by shunt revision with a high pressure valve with addition of anti siphon device, cranial expansion by subtemporal decompression without duroplasty, endoscopic third ventriculostomy or lumboperitoneal shunt with adjustable pressure valve.
9. Seizures: Seizures occurs in 5% of patients. If recurrent anticonvulsant therapy is required.
10. Subdural haematoma (SDH). This occurs in infants with large ventricles and thin cortical mantle (>2cms) and is treated by revision with high pressure valve or adjustable valve set to higher pressure. Burr hole evacuation of SDH may be required if symptomatic
11. Upward herniation of brainstem through tentorial hiatus, can happen if lateral ventricle is shunted in a posterior fossa lesion producing obstructive hydrocephalus. The clinical presentation is obtundation and pin point pupils. CT scan is diagnostic. This is treated by removal of shunt and excision of posterior fossa lesion.

Late complications

1. Abscess: Abscess results after meningitis due to shunt infection and is treated with tapping, removal of the shunt along with appropriate antibiotics.
2. Craniostenosis, microcephaly: Most common cranial malformation is dolicocephaly from sagittal synostosis and most are treated conservatively. Surgical treatment required rarely in case of cosmetic deformity or evidence of raised intracranial pressure. Extensive cranial moulding can happen after large head is shunted and is treated by appropriate positioning while lying down.
3. Tube disconnection/fracture: Tube fracture is common over clavicle which is the most mobile portion.
4. Blindness: Blindness may occur due to posterior cerebral artery infarct because of hydrocephalus/shunt malfunction due to transtentorial herniation, chronic papilledema. Younger patients have better visual recovery with early treatment of raised ICP.
5. Silicone allergy: CSF is initially sterile. It is treated by changing to polyurethane shunt material.
6. Metastasis: In case of shunting in medulloblastoma, ependymoma, certain pineal region tumours like endodermal sinus tumor filter incorporated shunt tubes may be used to avoid metastasis.
7. Ingunial hernia, hydrocele: This occurs if shunting is done before processus vaginalis closes and is treated by herniotomy.
8. Peritoneal pseudocyst: Peritoneal pseudocyst can present because of talc use during surgery and is treated by repositioning.
9. Length shortening: Length shortening can occur at

both inperitoneal or ventricular ends with growth of child as well as cerebral cortex expansion post shunting. It presents as signs of raised. ICP Shunt is revised.

10. TIP migration: Shunt tube wants to go where it wants to go is the saying. Luckily with improved hardware, incidence of shunt migration is less.
11. Valve resetting after MRI and head injury: It is advised to check pressure of the valve after every MRI exam information as well as after history of moderate/severe head injury.
12. Trapped fourth ventricle: Fourth ventricle can be appear dilated while other ventricle is shunted and appears normal. This usually happens in post-infectious cases. This condition presents with lower cranial nerve palsy, ataxia and obtundation. Shunting for fourth ventricle is done
13. Laproscopy in shunt: Lower carbon dioxide pressure of around 10 mmHg is used to prevent raised ICP during prolonged surgery. Hemoclip on distal shunt tip is applied and is removed at the end of surgery to prevent infection and pneumocephalus.
14. When to remove a shunt: This is a question most often asked. Shunt independence rarely happens in non-tumour cases and even patients who have been evaluated by radioisotope studies have eventually required shunt after few years.

Points to Remember

- ***Serial assessment of head circumference charting and matching it with age and sex matched graphs to identify hydrocephalus and early shunting in case of clinical signs and symptoms of raised ICP is advised.***
- ***Cognitive improvement is better with early shunting.***

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Date: 19th & 20th November, 2016

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PEDIATRIC NEUROLOGY

EPILEPTIC ENCEPHALOPATHIES IN CHILDREN

***Vinayan KP**

Abstract: *Childhood epileptic encephalopathic syndromes are a group of conditions in which cognitive, sensory and/or motor functions deteriorate as a consequence of epileptic activity. This terminology classically denotes a group of well-defined epileptic syndromes of childhood associated with a high probability of encephalopathic features that develop or worsen after the onset of epilepsy. However, it is increasingly being used in children who develop any deterioration/stagnation in development as a result of presumed epileptic activity. This phenomenon is most common and severe in infancy and early childhood. Evidence for the currently available therapeutic options in these difficult-to-treat epileptic syndromes is reviewed and a stepwise management strategy is suggested.*

Keywords: *Epileptic encephalopathy, Syndrome, Children, Treatment*

Epileptic encephalopathic syndromes were originally defined as a group of conditions in which cognitive, sensory and/or motor functions deteriorate as a consequence of epileptic activity. This may be due to frequent seizures and/or abnormal EEG activity.[1] Diagnosing epileptic encephalopathy in a child requires demonstration of a delay in the acquisition of developmental skills as compared to the peers or a regression in the already acquired abilities. According to the most recent International League Against Epilepsy (ILAE) document on the classification of epilepsies, epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone.[2] Over the years, the concept of epileptic encephalopathy has been used to define two differing scenarios. On one hand, the term characterizes a group of well defined epileptic syndromes of childhood associated with a high probability of encephalopathic features that may present or worsen after the onset of epilepsy. All children with these syndromes may not be encephalopathic; however, the risk is substantial. The same terminology is also used in children who develop a deterioration or stagnation in the development as a result of presumed epileptic activity. According to this concept, epileptic encephalopathy may present along a continuum of severity, occurring at any age. For example, a child with a focal cortical dysplasia may developmentally stagnate or deteriorate as a result of very frequent epileptic activity. This phenomenon is most common and severe in infancy and early childhood, when global and profound impairment may occur.

However, the exact cause of an apparent encephalopathy is usually unknown in a given child. It may be the product of the underlying cause, the result of epileptic activity in the brain, or a combination of both. The contribution of the antiepileptic drugs (AED) to the whole process is another controversial issue. In this review, the initial focus is on the well defined epileptic syndromes of childhood with a predisposition for encephalopathy and the different pathophysiological mechanisms contributing to the encephalopathic process, which is followed by a detailed discussion on the available therapeutic options for these difficult to treat disorders.

Classification

Different schemes have been used to classify the epileptic encephalopathic syndromes of childhood. The commonest approach is based on the age of onset of these disorders. The salient clinical features of each of these disorders are given in Table I. It should be noted that in a given child, the clinical and EEG characteristics depend on the age at onset, and may change over time, according to the successive age ranges. An alternative approach is based on the presumed pathophysiology of individual syndromes (Box 1). However, the relative contribution of each of the different pathophysiological processes to a specific syndrome is almost always speculative.

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Table I. Epileptic encephalopathic syndromes of infancy and childhood in the order of age of onset

(Modified from Wirrel et al., 2005)[3]

Syndrome	Age of onset	Seizure types /other clinical	EEG features
Early myoclonic encephalopathy (Aicardi)	Newborn	Prominent myoclonus, partial seizures, tonic spasms	Suppression-burst
Early infantile epileptic encephalopathy (Ohtahara syndrome)	New born	Tonic spasms, partial seizures	Suppression-burst
Migrating partial epilepsy in Infancy	1-7 months	Multifocal partial seizures	Multifocal rhythmic theta
West Syndrome	Peak 4-6 months	Infantile spasms	Hypsarrhythmia
Dravet syndrome	First year	Often prolonged partial or secondarily generalized seizures with hyperthermia, multifocal myoclonus usually after 1 year	Often normal at onset. Generalized polyspike and spike wave activated with photic stimulation after onset of myoclonus
Lennox-Gastaut Syndrome	Early childhood, peak 2-8 years	Tonic, atonic, atypical absence, myoclonic (rare)	Diffuse, frontally-predominant slow spike wave usually <2 Hz – often evolves over time. Frontal 10-12 Hz rhythms
Myoclonic-Astatic Epilepsy	Early childhood, 2-8 years	Myoclonic - astatic, myoclonic, atypical absence	2-3 Hz generalized spike-wave, photoparoxysmal response common. Parietal 4-7 Hz rhythms
Landau-Kleffner Syndrome	Early childhood, 3-8 years	Verbal auditory agnosia, 75% have seizures which are usually partial motor	Awake recording usually shows temporal spikes. In sleep, discharges become increasingly frequent and synchronous, and may be continuous
Continuous spike and waves in slow wave sleep (CSWS)	Early childhood, 3-8 years	Hyperkinesis, cognitive regression, generalized minor seizures, partial or secondarily generalized motor seizures	Electrical status epilepticus in slow sleep

Neurobiology of epileptic encephalopathies

The neurobiological mechanisms leading to the co-occurrence of epilepsy and developmental dysfunctions are depicted in Fig 1. Children with epilepsy are at increased risk for developmental deficits as a result of multiple mechanisms. Both neurodevelopmental disorders and epilepsy may be the expression of underlying structural brain lesions. These may be either congenital, like a diffuse cortical dysplasia or acquired as the sequelae of neonatal insults like hypoxic ischemic encephalopathy (HIE). Several genetic syndromes have cognitive disorders along with autistic behavior and refractory seizures as their defining clinical features. Angelman syndrome and tuberous sclerosis are classical examples. In such cases,

Box 1. Classification of epileptic encephalopathic syndromes of childhood based on presumed pathophysiology[1]

Epileptic encephalopathy associated with frequent/ severe seizures

Migrating partial epilepsy of infancy

Dravet syndrome

Epileptic encephalopathy with continuous/nearly continuous spike and slow wave activity

Ohtahara syndrome

Early myoclonic encephalopathy of Aicardi

West syndrome

Lennox Gastaut syndrome

Myoclonic astatic epilepsy

Landau- Kleffner syndrome

Continuous spike and wave in slow wave sleep (CSWS)

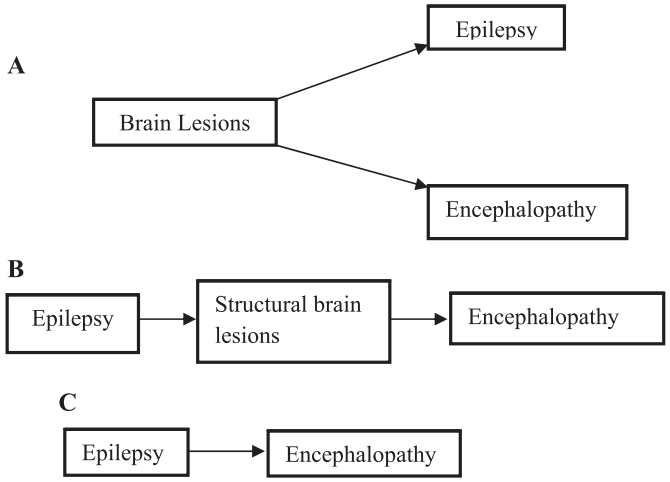

Fig 1. Co-occurrence of epilepsy and encephalopathy[4]

Fig 1a, b, c. Pathophysiology of epileptic encephalopathy

(A) Brain damage or dysfunction leads both to epilepsy and encephalopathy

(B) Epilepsy results in structural brain damage which, in turn, results in encephalopathy

(C) Epilepsy leading directly to encephalopathy without causing brain damage.

the relationship between the ongoing epilepsy and the encephalopathic course becomes highly complex. However, it has been documented that ongoing seizure activity may further retard the developmental progression in these situations.[5] Even these children may show meaningful cognitive improvement if seizure control or improvement in their EEG is achieved.

Animal studies have shown that recurrent seizures may result in long-term adverse effects on learning and memory. These changes are paralleled by changes in brain connectivity, dendritic morphology, excitatory and inhibitory receptor subunits, ion channels and neurogenesis. Surprisingly, these changes may occur even in the absence of overt cell loss.[5] Significant abnormalities have been documented even in intracellular functions of specific neurons after exposure to multiple seizures.

The effect of antiepileptic drugs on the developmental domains of a child with epilepsy is double edged. On one hand, it may reduce the number of overt and subtle epileptic seizures leading to the improvement in the cognitive and behavioral abilities and other learning processes. Reduction in the seizure count may in turn improve the psychosocial environment, providing an additional benefit to the child.[6] On the other hand, several case reports have shown time and again that cognitive processes are significantly affected by the intake of AEDs. It was difficult to demonstrate this effect through controlled studies due to various confounding variables. These effects may be seen maximally at higher doses of AEDs, during polytherapy or after prolonged intake of drugs. The problems may range from blurring of vision and diplopia due to minimal cerebellar dysfunction to excessive sedation and reduced psychomotor speed. However, it is extremely difficult to assess whether the changes in behavior are related to the de novo effect of antiepileptic drugs or to the changes in seizure control. In the so called 'release phenomenon', children with catastrophic epileptic syndromes with preexisting cognitive and behavior problems may experience a rapid improvement in arousal and abilities when their seizures are controlled. This improvement initially occurs without the required social skills and experience to use these new skills. As a result, these children suddenly appear hyperactive and uncontrollable.[7] This situation may be mistaken for an adverse effect of the AED.

Studies on the individual drugs are difficult to evaluate because of the small sample sizes along with a wide variation in the dosage and duration of treatment and the treated epileptic syndromes. Generally, all the AEDs have

the potential for affecting the cognitive and behavioral domains. Loring and Meador have reviewed the impact of individual antiepileptic drugs on cognitive abilities of children.[8] Phenobarbital is the agent most strongly implicated in the literature to cause cognitive impairment. In studies of infants with febrile seizures, phenobarbital was associated with a higher risk of memory, concentration, fine motor and behavioral problems. In one study comparing phenobarbital to placebo, mean IQ was seven points lower in the phenobarbital group after two years of treatment.[9] There are no comparative studies on the cognitive and behavioral side effects of the newer antiepileptic drugs in children. Cognitive side effects have been described in children receiving most of the newer antiepileptic drugs. While long-term use of antiepileptic medications may contribute partly to cognitive impairment, it is unlikely to be the major causative factor in children with epileptic encephalopathies.

Therapeutic perspectives

Concept of epileptic encephalopathy is firmly based on the belief that suppression of seizures and/or subclinical epileptic activity may improve cognition and behavior.[2] However, it should be admitted that most of the epileptic encephalopathic syndromes of childhood remain refractory to available therapeutic options. Developmental trajectory seldom becomes completely normal, even after the control of seizures. However, meaningful improvement in development may be achieved in children with frequent seizures, if the seizures and interictal epileptiform abnormalities were controlled relatively early in the clinical course. The United Kingdom infantile spasms study (UKISS), a prospective multicenter randomized trial comparing hormonal treatment and vigabatrin in children with infantile spasms, showed a trend towards better developmental outcome in children with cryptogenic infantile spasms who achieved seizure control relatively early.[10,11] In a recent clinical series, children with symptomatic focal epilepsies who had a good seizure outcome after successful epilepsy surgery showed an immediate and substantial gain in the cognitive abilities. However, the developmental curve tended to plateau after the initial spurt in many cases.[12] Authors concluded that the long term developmental outcome may be affected by decreased intellectual potential of genetic origin, irreversible epileptic damage to neural networks supporting cognitive function or reorganization plasticity after early focal lesions.

The currently available therapeutic options in epileptic encephalopathies include antiepileptic drugs, co-factors like pyridoxine, steroids, intravenous immunoglobulins, epilepsy surgery and ketogenic diet.

Antiepileptic drugs

Most of the epileptic encephalopathies remain resistant to conventional and newer antiepileptic drugs. Nonetheless, certain antiepileptic drugs have got a specific favourable response on some of the syndromes. At the same time, several AEDs have been found to exacerbate seizures and encephalopathy in certain individuals.

AEDs with specific actions

Vigabatrin

Elterman et al found that 52% of their 25 patients with infantile spasms associated with tuberous sclerosis responded to vigabatrin within two weeks of treatment compared with 16% of the 117 patients without tuberous sclerosis.[13] However, there have been reports of both asymptomatic and symptomatic visual field defects with loss of peripheral vision to varying degrees in adults and children treated with vigabatrin. This appears to occur most commonly in patients who have been treated with vigabatrin for more than six months. It does not appear to be reversible on withdrawal of vigabatrin. A recent Cochrane review meta-analysis concluded that vigabatrin may be effective in the treatment of infantile spasms due to tuberous sclerosis complex.[14] However, more prospective studies on the long-term developmental and epilepsy outcomes are required. This drug is not yet licensed in India.

Benzodiazepines

A single night time high-dose oral or rectal diazepam (1 mg/kg up to a maximum of 30 mg per dose) decreased nocturnal spiking in continuous spike and waves in slow wave sleep (CSWS) syndrome ,thus improving the encephalopathy.[15] Clobazam has also been shown to be effective in improving the spike burden in CSWS.[16] In our own case series (unpublished observation), around 80% of 15 children with CSWS showed good improvement in both clinical and EEG parameters when treated with high dose clobazam. However, the overall relapse rate after treatment with benzodiazepines remains relatively high.[17] Ethosuximide has been shown to be beneficial in such resistant CSWS.

Stiripentol

Stiripentol has been demonstrated in a double-blind, placebo controlled study to be efficacious in Dravet syndrome. When added to clobazam or valproic acid, 71%

of children receiving stiripentol versus only 5% of the placebo group experienced a greater than 50% reduction in seizure frequency and 43% of the stiripentol group achieved complete control of tonic-clonic seizures.[18] In another open label therapeutic trial of Dravet syndrome from Japan, more than 50% reduction in seizures was reported in 61% of children on stiripentol compared to only 15% of children on any of the 15 conventional AEDS.[19] This drug is not licensed in India for clinical use.

AEDs which may exacerbate the seizures and encephalopathy

Carbamazepine is the most commonly implicated AED in the exacerbation of seizures and encephalopathy in several idiopathic focal epilepsies and symptomatic generalized epileptic encephalopathies of childhood. This drug should be avoided in cases with bilateral synchronous spike and wave discharges of 2.5-3 Hz, and used with caution in children with mixed seizure disorders.[3] It may aggravate absence, myoclonic and atonic seizures and provoke non-convulsive status epilepticus. It may also worsen myoclonic seizures in Angelman syndrome and may exacerbate Landau-Kleffner syndrome, electrical status epilepticus in slow sleep and atypical benign partial epilepsy.[20] Phenytoin may exacerbate absence and myoclonic seizures in Lennox Gastaut Syndrome (LGS). Lamotrigine, carbamazepine and vigabatrin exacerbate both convulsive seizures and myoclonus in children with Dravet syndrome.[21]

Pyridoxine

Pyridoxine is a coenzyme of glutamic acid decarboxylase and enhances GABA synthesis. Low levels of GABA have been noted in cerebrospinal fluid of some infants with West syndrome. Pyridoxine is the initial treatment of choice for infantile spasms in Japan.[22] The dosage ranges from 100-300 mg/kg/ day for one week. The response rate is better for cryptogenic cases. As per our departmental therapeutic protocol, an initial trial with pyridoxine is offered for all children with West syndrome before proceeding with hormonal treatment. Side effects of high-dose pyridoxine include loss of appetite, irritability and vomiting. A therapeutic trial with other cofactors like folinic acid and pyridoxal phosphate may also be useful in infantile epileptic encephalopathies of unknown cause.

Adrenocorticotrophic hormone (ACTH) and oral steroids

ACTH and oral corticosteroids were used as the initial therapeutic choice in West syndrome. However, the choice of the preparation of ACTH (synthetic vs. natural) and the dosage (high vs. low) varies across studies and centers. The UKISS compared the efficacy of hormonal treatment to vigabatrin in the treatment of West syndrome not associated with tuberous sclerosis. 107 children with West syndrome were randomly enrolled to receive either vigabatrin (n = 52) or hormonal treatment (oral prednisolone n = 30, ACTH n = 25). Vigabatrin was given orally in two divided doses per day (50 mg/kg per day for the first two doses; increasing to 100 mg/kg per day after 24 h and, if spasms continued, to 150 mg/kg per day after 96 h from the start of treatment). Prednisolone was given orally (10 mg four times a day for 2 weeks, increasing to 20 mg three times a day after 1 week if spasms continued). Synthetic ACTH depot was given intramuscularly [0·5 mg (40 IU) on alternate days for 2 weeks, and increased to 0·75 mg (60 IU) on alternate days after 1 week if seizure control had not been achieved]. Proportions with no spasms on days 13 and 14 were: 40 (73%) of 55 infants assigned hormonal treatments [prednisolone 21/30 (70%), tetracosactide 19/25 (76%) and 28 (54%) of 52 infants assigned vigabatrin (difference 19%, 95% CI 1% - 36%, p = 0·043)].[23] However, at 14 months, there was no difference in seizure and developmental outcomes between the 2 groups.[11] 77 children were followed up to 4 years and both treatment groups were similar in both seizure and developmental outcomes.[10]

The UKISS trial was underpowered for subgroup analysis. However, a better developmental outcome was noted in children with cryptogenic West syndrome who were allocated hormonal treatment. The recently published US consensus opinion favors natural ACTH as the initial therapy for infantile spasms.[24] Larger prospective cohorts are needed to provide further therapeutic answers in this etiologically heterogeneous syndrome.

Traditionally, steroids are also being used in Landau-Kleffner syndrome/CSWS and less commonly, in other epileptic encephalopathies. Although steroids are considered standard treatment for Landau-Kleffner syndrome/CSWS, the efficacy of this therapy has only been suggested in case series rather than documented controlled trials. These disorders are difficult to study due to large fluctuations in their clinical course, often poor correlation between the severity of language impairment, EEG abnormalities and clinical seizures.[3]

Intravenous immunoglobulins

Intravenous immunoglobulins (IVIG) were used with benefit in several small clinical series of CSWS syndrome which were not responsive to steroid administration. However, the dosage and duration varies across the

Box 2. Epileptic encephalopathies: Principles of management

- Make a tentative diagnosis of epileptic syndrome and initiate the drugs with the most specific action for that syndrome relatively early in the course.
- Avoid the drugs which may worsen the clinical picture.
- Evaluate for a focal cerebral lesion causing the seizures and consider surgical option as early as possible
- Alternative therapeutic options like ketogenic diet may be considered early in children with diffuse/multifocal cerebral pathology and for those with no identifiable lesions.
- Successful therapeutic outcome includes both good control of seizures and maintenance of an optimal development.
- Early seizure control is associated with the best developmental outcome.

treatment groups. Mikati, et al showed a statistical trend for improved outcome in a group of 37 children with epileptic encephalopathies treated with IVIG and followed up for a mean period of 15 months.[25] Several acute epileptic encephalopathies of childhood, refractory to conventional medical therapy, were recently described to be associated with immune mechanisms.[26] Intravenous immunoglobulins may be useful in such cases in controlling the inflammatory response.

Epilepsy surgery

Several case reports and clinical series have reported the utility of surgical option in medically refractory epileptic encephalopathies of infancy and childhood.[12] Early surgical intervention may potentially alter the developmental trajectory in refractory epilepsies.[27] Palliative procedures like corpus callosotomy and vagus nerve stimulation may be useful options in children with refractory epileptic encephalopathies of multifocal origin. Multiple subpial transection (MST) has been reported to be effective in some patients with refractory Landau-Kleffner syndrome.

Ketogenic diet

The ketogenic diet (KD) mimics the biochemical response to starvation, when ketone bodies become the main fuel for the brain energy demand.[28] In patients with medically refractory epilepsy or severe intolerance to antiepileptic drugs (AEDs), KD is a potentially effective alternative. The efficacy of the ketogenic diet in children with epileptic encephalopathies is difficult to determine as most efficacy studies have not analyzed the outcome in specific syndromes. Some evidence indicates that patients with Dravet syndrome[29] and myoclonic–astatic epilepsy may respond positively to the prescribed diet.[30] Principles of management of epileptic encephalopathies shown in Box 2.

Conclusions and therapeutic recommendations

Epileptic encephalopathic syndromes are a group of etiologically heterogeneous disorders clinically characterized by cognitive and behavioral delay or regression usually associated with refractory seizures, predominantly affecting the developing brain. Inherent in the concept is the notion that suppression of seizures and/or interictal abnormalities may improve the developmental outcome. However, many of the well defined epileptic encephalopathies still remain refractory to the available therapeutic options with relentless decline in the developmental outcome. There is an urgent need for further focused research to improve the therapeutic outcome for these disorders.

Points to remember

- ***Childhood epileptic encephalopathic syndromes are a group of resistant epilepsies in which cognitive, sensory, and/or motor functions deteriorate as a consequence of epileptic activity.***
- ***This deterioration may be the product of the underlying cause, the result of epileptic activity in the brain, or a combination of both.***
- ***The currently available therapeutic options in epileptic encephalopathies include antiepileptic drugs, co-factors like pyridoxine, steroids, intravenous immunoglobulins, epilepsy surgery and ketogenic diet.***
- ***Children with epileptic encephalopathic syndromes may need early and aggressive management in a specialized center for the optimal developmental outcome.***

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PEDIATRIC NEUROLOGY

NEUROMETABOLIC DISORDERS: A DIAGNOSTIC APPROACH

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Abstract: *Inherited neurometabolic disorders constitute an important group of genetic disorders with diverse neurological manifestations. Many of them are amenable for treatment and early intervention is necessary to prevent or ameliorate the extent of brain damage. However, the diagnosis and management of these disorders are often challenging to the clinicians in view of the overlapping and non-specific phenotypes. A systematic diagnostic approach often helps in narrowing down the differential diagnoses and plan appropriate investigations. This review presents a symptom-based approach for diagnosis of common metabolic disorders encountered in clinical practice.*

Keywords: *Neurometabolic disorders, Inborn errors of metabolism, Epilepsy, Children.*

Inherited neurometabolic disorders constitute almost seven hundred different rare genetic diseases which can affect the brain from birth to adulthood.[1] These disorders present with diverse neurological manifestations and many of them are associated with irreversible brain injury.[2] It is important to make an early diagnosis since timely intervention can either prevent or ameliorate the extent of brain damage in certain metabolic disorders.[3] The therapeutic goals include improvement and/or stabilization of psychomotor or cognitive development, behaviour or psychiatric disturbances, seizures and other neurologic or systemic manifestations.[3,4] However, the diagnosis and management of these disorders is often challenging to clinicians because of the rarity and phenotypic variability. The frequency of neurometabolic disorders varies among different populations and higher rate of consanguinity results in a significantly higher incidence of the disease.[1] Higher rate of consanguinity in certain parts of India makes it imperative for physicians to be familiar with the diagnosis and management of these disorders. This review focuses on a practical clinical approach to diagnosis in children with suspected metabolic disorder. A symptom-based approach is adopted to facilitate formulation of differential diagnoses and planning of investigations rather than description of individual disorders.

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Clinical approach

The symptoms and signs of neurometabolic disorders are protean and non-specific and a systematic approach is needed in order to arrive at a diagnosis. Clinical history needs to be analyzed considering the following points (a) Age at onset and clinical presentation, (b) Pattern of inheritance, (c) Key clinical symptoms and signs with special focus on sites of neuraxis and extra-neural involvement, (d) Course of the disease and (e) Severity of impairment.

Age at onset of the symptoms

Metabolic or genetic disorders have a variable phenotype and imaging features, depending on the age at onset. If the patient has a baseline developmental delay, the age at onset of the neurological symptom or regression is regarded as the age of onset. It is useful to classify the disorders into broad groups such as infancy (1-12 months), late infantile/early juvenile onset period (1-5 years), early infantile, late infantile / early juvenile and late childhood period (5-15 years).[5] The clinical presentation and the imaging features of the same disease in each age group vary and one has to be familiar with the variable presentation of these disorders in different age groups. For example, Tay sachs disease or infantile GM2 gangliosidosis present with neuroregression and exaggerated startle response to sounds whereas the presentation of juvenile onset GM2 gangliosidosis includes neuroregression, gait difficulty, ataxia, peripheral neuropathy and psychosis.[6-8] The classical early infantile Krabbe leukodystrophy presents with regression, irritable cry and opisthotonic posturing.[9] On the other hand juvenile onset Krabbe leukodystrophy presents with spastic paraparesis or visual impairment.[10] The magnetic resonance imaging (MRI) findings also vary in different age groups.[11]

The two features that mostly suggest a progressive nature of the disorders are a) the gradual loss of previously acquired milestones or intellectual abilities and b) the development of neurological signs and symptoms following a normal or delayed period of development and these features are more easily identified when the onset is later with more rapid deterioration. Considerable diagnostic delay occurs when disorders have a very early onset or develop very slowly.

In the new born period, the symptoms may be non-specific such as respiratory distress, hypotonia, poor sucking, vomiting, dehydration, lethargy and seizures.[12] Typical clinical scenario is that of a full term baby born after a normal pregnancy and delivery presenting with relentless deterioration after an initial symptom free interval. An abnormal urine and body odour occur in certain diseases e.g. maple syrup odour in maple syrup urine disease, sweaty feet odour of isovaleric acidemia and type II glutaric aciduria.

Family history and pattern of inheritance

A careful family history is fundamental to the evaluation of children with metabolic disorder. Presence of positive family history or other potentially relevant neurological impairment is to be enquired and documented if present. Autosomal dominant traits may be present in successive generations, although the degree of expressivity may vary whereas autosomal recessive traits often do not manifest in successive generations but may be present in siblings. X-linked recessive conditions manifest in male siblings, male first cousins and maternal uncles e.g., X-linked adrenoleukodystrophy.

Almost 90% of metabolic disorders have autosomal recessive inheritance. Because of the small sibships, cases appear to be sporadic at times. A family history of unexplained neonatal or infantile death should be enquired. Few conditions have an X-linked inheritance such as adrenoleukodystrophy, Fabry's disease and Lesch- Nyhan disease. A maternal inheritance suggests mitochondrial disorder and it is to be remembered that mitochondrial disorders can also follow a Mendelian pattern of inheritance. Sometimes apparent autosomal inheritance pattern may mask a maternal inheritance.[13]

Course of the disease

Detailed developmental history should be obtained to define acquisition or loss of skills, age and pattern of onset namely acute and insidious onset or episodic progression of symptoms. A sudden and catastrophic onset, with relapses and remissions, relations to infection, fasting and particular food intake, non-specific physical findings and a good response to symptomatic therapy often points to defect in intermediary metabolism such as aminoacidopathies, organic acidemias and fatty acid oxidation disorders.[14] On the other hand, a gradual onset, symptoms that are permanent and progressive and symptoms and signs which are independent of intercurrent events are often suggestive of organelle disorders such as lysosomal storage disorders and peroxisomal disorders.[14] There are exceptions to this generalization. For example, Leigh disease which is an organelle disorder is characterized by sudden onset of encephalopathy and episodic course.

It is important to remember that a variety of metabolic and genetic conditions may exist in patients who were initially diagnosed to have a static encephalopathy. Clinical pointers which warrant further evaluation in these children with cerebral palsy mimics are absence of definite perinatal injury, a positive family history, inadequately explained oculomotor disturbances, involuntary movements and ataxia.[15]

Pattern of involvement

Even though the metabolic insult is global, some of the disorders have striking anatomical pattern of involvement.[2] Clinically these disorders can be classified according to the part of the central nervous system predominantly affected such as cortical gray matter, white matter, or both, basal ganglia and cerebellum and the classification facilitates diagnosis.

On analyzing the history, the key neurological symptoms of the patient are to be identified for a syndromic diagnosis. One should know whether the primary symptoms and signs are related to (a) gray matter involvement such as seizures, visual impairment and cognitive decline (b) white matter involvement such as gait difficulty, abnormalities in tone (spasticity/hypotonia), (c) behavioural or psychiatric manifestations (aggression, irritability, anxiety) and (d) extrapyramidal system involvement (dystonia, tremor, choreo-athetosis, parkinsonian).

The associated complaints such as enlarging head, exaggerated startle response to sound, incessant crying, skin manifestations, visual disturbances, deafness and oculomotor disturbances should be looked for. One should determine if the clinical presentation is exclusively neurological or neurologcial findings are part of a systemic disease.

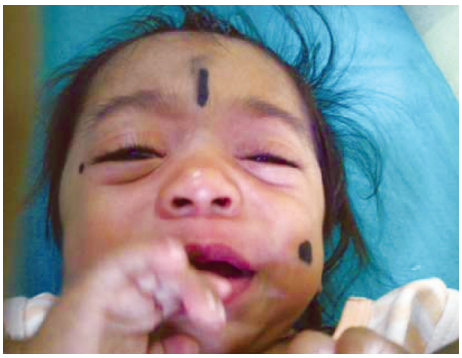


Fig.1a. Infantile GM1 gangliosidosis - coarse facial features and puffy eyelids

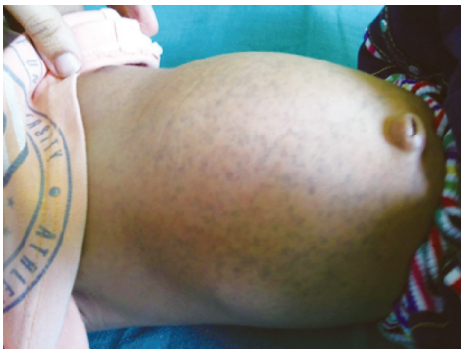
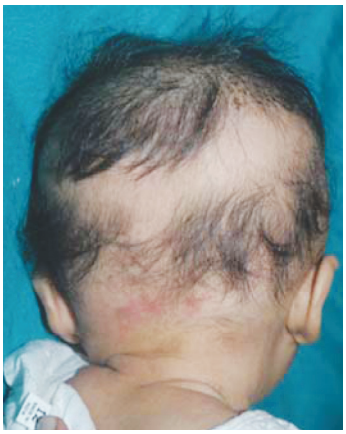


Fig.1b. Extensive cutaneous melanosis



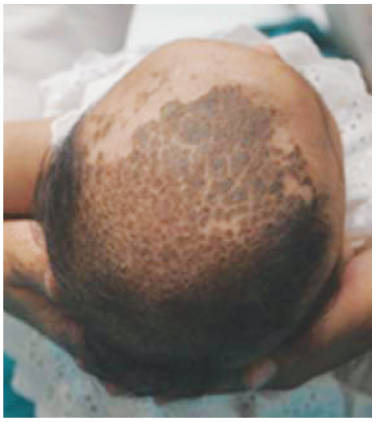


Fig.2 a & b. Biotinidase deficiency – scalp alopecia and seborrhea

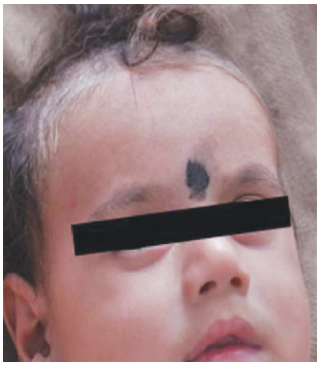


Fig.2 c. Menkes syndrome - hypopigmented hair

Examination

The child should be screened first for any evidence of systemic diseases by a good head to foot examination and careful recording of anthropometric measurements. Dysmorphic features of the face, fingers, toes, extremities, spine, or internal organs are suggestive of prenatal onset. Coarse facial features are seen in mucopolysaccharidoses, mucolipidoses, GM1 gangliosidoses (Fig.1a and b] and glycoprotein syndromes like fucosidosis.Children with hyperhomocystinuria have marfanoid habitus.

The abnormalities of skin and hair can give useful clues to the diagnosis of systemic diseases with neurological manifestations. Hypopigmented sparse hair, alopecia and recurrent skin rashes in a child with regression and refractory seizures suggest a diagnosis of biotinidase deficiency (Fig.2a and b). A child with a hypopigmented kinky hair, seborrheic dermatitis and epilepsy and regression in early infancy straight away gives a diagnosis of Menkes disease (Fig.2c). Examination of the skin for icthyosis and angiokeratomas are important. Presence of

the former may indicate Sjogren Larsson syndrome in a child having spastic paraplegia and leukoencephalopathy on MRI. Angiokeratomas are observed both in fucosidosis and Fabry's disease. Cutaneous melanosis is another important clinical clue in patients with lysosomal storage disorders especially GM1 gangliosidosis (Fig.1b). Hypertrichosis is a feature of mitochondrial disorders, especially in *SURF1* positive Leigh disease. Hyperpigmentation of the oral mucosa, genitalia and umbilicus in a child with regression of milestones may suggest a diagnosis of adrenoleukodystrophy.

Measurement of head circumference and velocity of growth is needed to identify megalencephaly or microcephaly. It is an essential part of neurological examination and may provide vital diagnostic clues. Macrocephaly with startle response to sound and regression at around six months of age suggest a diagnosis of GM2 gangliosidosis (Fig.3a). Macrocephaly, extreme irritability, incessant crying, opisthotonic posturing and regression are diagnostic clues for Krabbe disease. Episodic regression following febrile illnesses especially minor diarrhoeal illness, macrocephaly and dystonia are seen in glutaric aciduria type 1 (Fig.3b). In a child with suspected leukodystrophy, a large head suggests a number of diagnosis viz. Canavan's disease, Alexander disease, megalencephalic leukodystrophy with subcortical cysts. Macrocephaly can also be seen in another important late onset metabolic disorder namely L-2 hydroxy glutaric aciduria where MRI shows evidence of leukoencephalopathy.[16]

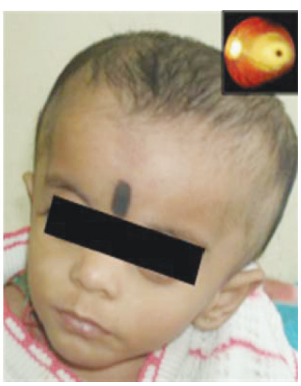


Fig.3a. Tay Sachs disease - macrocephaly. Inset shows cherry red spot

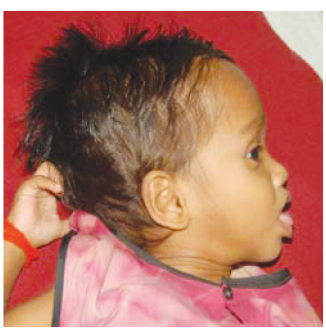


Fig.3b. Type 1 Glutaric aciduria - macrocephaly and generalized dystonia

The eye is considered as a window to the brain, making fundus examination an integral part of evaluation of these children.[17] The important points to be looked for are presence of cataract, lens dislocation, corneal clouding, retinitis pigmentosa, optic atrophy and cherry red spots. In those children presenting with progressive extrapyramidal signs, the importance of looking for the Kayser Fleisher ring to establish Wilson disease needs to be emphasized. Presence of lens dislocation in a child with refractory neonatal onset epilepsy should alert the physician to consider the possibility of isolated sulfite oxidase deficiency and molybdenum co-factor deficiency.[18,19] Lens dislocation in a child with mental retadation, behavioural disturbances and marfanoid habitus are clues to the diagnosis of homocystinuria. Retinal pigmentary defects are seen in mitochondrial disorders, neuronal ceroid lipofuscinoses and peroxisomal biogenesis disorders. Cherry red spots are usually noted in lysosomal storage disorders such as Tay Sachs disease, Niemann Pick type C disease and GM1 gangliosidosis. Corneal clouding is noted in mucopolysaccharidoses or mucolipidosis. A rare but important disorder which will present to the neurologist is mucolipidosis type 4 in which corneal clouding can be associated with ptosis, oculomotor disturbances, retinal degeneration, optic atrophy and a spastic ataxic syndrome.[20] A thin corpus callosum and variable degree of hypomyelination are seen on MRI.[21] Visceromegaly and skeletal manifestations are characteristically absent in these children.[20]

A detailed neurological examination is then done to delineate or confirm the clinical syndromes identified in the history. The part of the neuraxis that is predominantly involved should be ascertained and categorised as disorders with epilepsy, extra pyramidal disorder, ataxia, spastic paraplegia/quadriplegia, psychiatric or behavioural presentation. The important clinical syndromes and the differential diagnoses to be considered are given below. For easy understanding the relevant confirmatory tests and the MRI findings are discussed along with the diseases rather than in a separate heading.

Epilepsy: Epilepsy is a frequent symptom in many metabolic disorders and sometimes dominates the clinical picture.[22] Epilepsy in children with metabolic disorders are

Table I. Neurometabolic disorders with epilepsy as the main manifestation[5]

Diagnosis	Onset	Clinical features	Diagnostic evaluation
Glycine encephalopathy	Neonatal period to early infancy	Myoclonic jerks, infantile spasms	Elevated glycine on TMS and quantitative estimation of amino acids MRI- corpus callosal thinning, defects, characteristic diffusion pattern, glycine peak on MRS.
Isolated sulfite oxidase/Molybdenum cofactor deficiency	Neonatal period to early infancy	Presentation similar to hypoxic ischemic encephalopathy, refractory seizures, facial dysmorphism, lens dislocation	Low serum uric acid, homocystine, positive urine sulphite testing, MRI- cystic leukomalacia, and cerebellar hypoplasia
Maple syrup urine disease	Neonatal period to early infancy	Encephalopathy, seizures, abnormal smell of the body and urine	Elevated branched chain amino acids on TMS, urinary DNPH test-positive, MRI- Leukoencephalopathy with characteristic diffusion pattern
Phenylketonuria	Early infancy to childhood	Infantile spasms, hypopigmented hair, abnormal smell of urine, microcephaly	Elevated phenylalanine on TMS/HPLC, positive ferric chloride and DNPH test, MRI- leukoencephalopathy
Menkes kinky hair syndrome	Early infancy to childhood	Focal clonic seizures, infantile spasms, myoclonic seizures hypopigmented kinky and friable hair, hypotonia, seborrheic dermatitis	Low serum copper and ceruloplasmin levels, hair microscopy-pili torti, MRI- cerebral atrophy, delayed myelination MRA-characteristic tortuous vessels
Biotinidase deficiency	Early infancy	Infantile spasms, refractory myoclonic seizures, alopecia, hypopigmentation of hair	Elevated C5-OH levels on TMS, elevated beta hydroxyl isovalerate, methyl citrate, and beta hydroxy propionate and lactate on urinary organic acid analysis, MRI- hypomyelination, dramatic response to biotin
Progressive neuronal degeneration [Alpers disease/ polymerase gamma (POLG) related disorder]	Late infancy to early childhood	Seizures, myoclonic jerks, transient hemiplegia, fatal hepatic encephalopathy especially after sodium valproate use	Elevated liver enzymes, MRI- cortical signal changes in the occipital area, variable basal ganglia and thalamic signal changes, *POLG1* genetic studies

Diagnosis	Onset	Clinical features	Diagnostic evaluation
Progressive Myoclonic Epilepsy syndromes			
Neuronal ceroid lipofuscinosis	Infantile, late infantile, juvenile and adult onset forms	Rapidly advancing psychomotor retardation, ataxia, blindness, myoclonic jerks, retinitis pigmentosa, optic atrophy	Giant somatosensory evoked potential, MRI- cerebral and cerebellar atrophy with periventricular signal changes, electron microscopy of axillary skin shows characteristic inclusions
Cherry red spot myoclonus syndrome	Late childhood to adolescence	GTCS, myoclonic jerks, ataxia, cherry red spot	Giant somatosensory evoked potential, MRI-normal, Bone marrow-storage cells.
Myoclonic epilepsy ragged red fiber (MERRF) syndrome	Late childhood to adolescence and adult hood	Ataxia, intention tremor, muscular weakness, optic atrophy, deafness	Elevated lactate, muscle biopsy- ragged red and blue fibers
Nieman Pick type C disease	Late childhood	Myoclonic seizures, ataxia, non-epileptic drop attacks (cataplexy), supranuclear vertical gaze palsy, splenomegaly	Bone marrow examination for storage cells, MRI-cerebellar atrophy, genetic testing
Gaucher disease type III	Late childhood (7-10 yrs)	Myoclonic epilepsy, psychomotor retardation, splenomegaly, osseous signs	Bone marrow examination, Glucocerebrosidase enzyme estimation
Late onset GM2 gangliosidosis	4-10yrs	Ataxia, myoclonic jerks, cherry red spots	Serum hexosaminidase levels

*TMS - Tandem mass spectrometry, HPLC- High performance liquid chromatography

MRS - Magnetic resonance spectroscopy

often associated with developmental delay, mental retardation and other neurological symptoms.The important disorders in this group are shown in Table I.

Movement disorder: Many metabolic disorders are associated with a movement disorder. The extrapyramidal disorder can be in the form of dystonic disorder, hyperkinetic movement disorder/choreo-athetosis or a parkinsonian disorder characterised by rigidity, tremor and slowness of movements. Predominant movement disorder observed is dystonia. The different patterns of involvement of the basal ganglia on neuroimaging often helps in formulating the differential diagnosis. The differential diagnosis depends on the age of onset of the symptoms. The common and the important differential diagnoses in this group of children are given in Table II.

Psychiatric/Behavioural manifestations: Only very few disorders present with isolated arrest or regression of psychic and perceptual functions without significant neurologic and extraneurologic signs. Pure psychiatric presentations characterised by behavioural disturbances (personality and character changes), loss of speech, scholastic failure, mental regression, dementia, psychosis and schizophrenia like symptoms can be the presenting manifestation of neurological disorders such as Sanfilippo

Table II. Neurometabolic disorders presenting with predominant extrapyramidal features[5]

Diagnosis	Onset	Clinical signs	Diagnostic evaluation
Glutaric aciduria Type1	Late infancy to early childhood	Acute onset pseudoencephalitis presentation, choreoathetosis, dystonia	Elevated glutaryl carnitine on TMS and urinary organic acid analysis MRI- basal ganglia signal changes and hypomyelination, subdural hematoma,'anterior temporal lobe cysts' leading to 'bat wing appearance'
Methyl malonic acidemia	New born period, infancy to early childhood	Episodic encephalopathy, neutropenia, thrombocytopenia, candidiasis, movement disorder, hypotonia, cyclic vomiting,	Elevated methylmalonic acid, methylcitrate, propionic acid and 3-hydroxypropionate levels on urinary organic acid analysis, MRI-medial globus pallidus signal changes
Propionic acidemia	New born period, Late infancy to early childhood	Episodic encephalopathy, dystonia, choreoathetosis	Elevated propionyl carnitine on TMS and urinary organic acids, MRI-Bilateral caudate and putamen signal changes, cortical hyper intensities
Leigh disease	Late infancy to early childhood	Episodic encephalopathy, mental regression, breathing difficulties, oculomotor disturbances, optic atrophy, dystonia, choreo-athetosis, ataxia, peripheral neuropathy	Raised serum lactate, MRI- basal ganglia, brainstem and cerebellar signal intensity changes, muscle biopsy- cox deficient fibers
Lesch-Nyhan syndrome	Early infancy	Choreo-athetosis, self mutilation	Hyperuricemia
Wilsons disease	5-15years	Dystonia, tremor, parkinsonian features, scholastic failure, psychiatric abnormalities, liver involvement	Slit lamp examination for KF ring, low serum Cu and ceruloplasmin MRI- basal ganglia,thalamus and brainstem involvement
Classic homocystinuria	5-15years	Lens dislocation, moderate mental retardation, Marfanoid habitus	Urine notroprusside test, serum homocystine levels high
Biotin responsive basal ganglia disease	5-15years	Episodic encephalopathy, dystonia, myoclonus	MRI-bilateral caudate and putaminal hyper intensity, dramatic clinical response to trial of biotin, SLC19A3 testing
Nieman Pick type C disease (Dystonic lipidosis)	1-5years.	Dystonia, ataxia, vertical gaze palsy, seizures, splenomegaly	Bone marrow examination for storage cells. MRI-cerebellar atrophy
GM1 Gangliosidosis	1-5years	Progressive dystonia especially orofacial dyskinesias, cognitive decline	'Pseudo gaucher' cells on bone marrow examination, beta galactosidase levels, MRI-hypomyelination with ganglionic signal changes

* TMS- Tandem mass spectrometry

Table III. Neurometabolic disorders presenting with spastic paraparesis[5]

Diagnosis	Age at onset	Additional Clinical Signs	Evaluation
Small molecule disorders			
Arginase deficiency	Early childhood	Episodic encephalopathy, seizures, often triggered by high protein intake	Hyperargininemia on TMS and HPLC studies (hyperammoninemia is inconstant)
Phenylketonuria	Adolescence	Optic atrophy, cognitive decline, seizures	Hyperphenylalaninemia, leukoencephalopathy on MRI
HHH syndrome	Late childhood	Episodic encephalopathy triggered by high protein intake or situations of protein catabolism, ataxia	Hyperammonemia, hyperornithinemia, homocitrullinuria
Biotinidase deficiency	Late onset	Bilateral optic atrophy, deafness, alopecia, seborrheic dermatitis	High lactate, elevated CS - OH levels on TMS, elevated excretion of 3-hydroxyisovaleric, lactic and 3-hydroxypropionic acids and 3-methylcrotonylglycine by urine organic acid analysis, low serum biotinidase levels
Hyperhomocystinemia	Adolescence to adult hood	Psychiatric manifestations, thromboembolic events, polyneuropathy	Hyperhomocysteinemia, hypomethioninemia, methylmalonic aciduria
Complex molecule disorders			
Adrenomyeloneuropathy	Adolescence to adult	Spastic para paresis, sensory signs, adrenal insufficiency	Elevated very long chain fatty acids
Late onset metachromatic leukodystrophy	Juvenile and adult onset	Psychiatric manifestations, polyneuropathy	Low aryl sulfatase levels, MRI-leukodystrophy
Krabbe disease	Juvenile	May have a hemi-paretic onset, ataxia,	Low galactocerebrosidase levels MRI- leukodystrophy, isolated pyramidal tract involvement

Cerebrotendinous xanthomatosis	Adolescence to adulthood	Juvenile cataract, xanthomas, cerebellar ataxia, chronic diarrhoea	MRI- leukoencephalopathy, dentate and pallidal signal changes
Sjogren Larsson syndrome	Juvenile and adult onset	Icthyosis, mental retardation, macular dystrophy	MRI- leukoencephalopathy with a lipid peak on MRS

TMS - Tandem mass spectrometry

HPLC - High performance liquid chromatography

disease, X-linked adrenoleukodystrophy, Wilson's disease, classic homocystinuria, juvenile onset metachromatic leukodystrophy and juvenile onset GM2 gangliosidosis. These children usually seek consultation from psychiatrists first and diagnostic delays are common. It is to be remembered that Sanfilippo disease or mucopolysaccharidosis Type 3, characterised by regression of high level achievements, loss of speech and extreme agitation, may not have obvious coarse facial features or visceromegaly. But hirsuitism and mild coarse facial features are common.

Spastic paraplegia/quadriplegia: This group is mainly constituted by disorders with dominant white matter involvement. Motor neurons and pyramidal tract are particularly vulnerable to degenerative and metabolic disorders because of the peculiar transport and energy requirements.[23] The diagnosis of these metabolic causes, is important for instituting specific treatments as well as genetic counseling. The important differential diagnoses in this group are shown in Table III.

A combination of lower motor neuron and upper motor neuron signs such as spasticity and diminished jerks or hypotonia with brisk reflexes and extensor plantar responses may indicate associated peripheral nerve involvement. Evidence of a demyelinating peripheral neuropathy is almost invariably seen in patients with metachromatic leukodystrophy.[24] Peripheral neuropathy is also an associated finding in Krabbe leukodystrophy.[25]

Ataxia or incoordination: Metabolic disorders are less frequent cause of ataxia and can be clinically classified based on the evolution of symptoms as intermittent or episodic, stable or progressive ataxias. Ataxia is frequent in acute or subacute decompensation of aminoacidurias, organic acidurias and urea cycle disorders.[26] Other causes of intermittent ataxia include respiratory chain disorders especially neuropathy, ataxia, retinitis pigmentosa (NARP) syndrome, pyruvate dehydrogenase deficiency, biotinidase deficiency and Hartnup disease. Fever sensitive ataxia is a feature of mild pyruvate dehydrogenase deficiency.[27] Glucose transporter deficiency may present with intermittent ataxia which worsens before meals.[28]

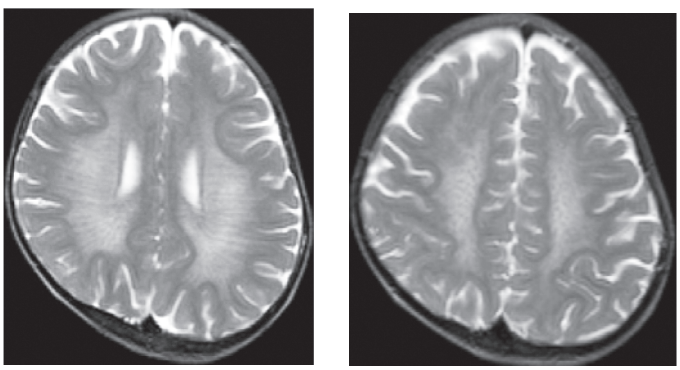
Progressive spinocerebellar dysfunction is a feature of ataxia with vitamin E deficiency, abetalipoproteinemia, cerebrotendinous xanthamatosis and mitochondrial depletion syndromes. Cerebellar ataxia in the context of progressive mental deterioration is seen in many late onset lysosomal storage disorders such as late onset gangliosidoses, Krabbe disease, metachromatic leukodystrophy, Niemann-Pick type C disease and galactosialidosis, abetalipoproteinemia and Refsum disease. Respiratory chain disorders present as ataxia predominantly. L-2 hydroxy glutaric aciduria is a metabolic disorder which can present with ataxia, macrocephaly and seizures in the adolescent age group.

Diagnostic evaluation

Diagnostic evaluation in children with neurometabolic disorders should be tailored to the presentation and should proceed from the least to most invasive investigation. Initial evaluation includes complete blood counts, serum ammonia, lactate, screening of the urine for abnormal metabolites, tandem mass spectrometry for aminoacids, plasma and urine acyl carnitine profiles, magnetic resonance imaging, electroencephalography and a formal ophthalmological evaluation. The results of these tests will often suggest the need for specialised electrophysiological, metabolic and genetic testing. A systematic biochemical approach to these disorders is often helpful to narrow down the differential diagnosis.[5,29]

Neuroimaging facilities are widely available and magnetic resonance imaging has thus emerged as a useful technique for the initial stages of evaluation. Most often, imaging will be the most readily available investigation rather than the biochemical tests. A combined clinical and imaging approach may help in narrowing down the differential diagnoses better than clinical syndromes alone. It is important to review the magnetic resonance imaging studies with respect to the expected myelin development for the patient's age. The main areas of involvement need to be analyzed and categorized as white matter, cortex, deep ganglionic structure (basal ganglia, thalamus), brain stem and cerebellar involvement. A pattern recognition approach can be applied to the MRI diagnosis of leukoencephalopathies which can direct further investigations e.g., bilateral symmetrical signal changes in the periventricular and deep white matter sparing the subcortical 'U' fibers is a feature of metachromatic leukodystrophy.[30] The spared hypointense radially oriented white matter and dots within the hyperintense white matter may resemble the skin of tiger (radial stripes) and leopard dots. (Figs.4a and b). It is again emphasized that the magnetic resonance imaging findings vary depending on the age of presentation. MRI in infantile onset Krabbe leukodystrophy shows bilateral optic nerve hypertrophy in addition to the bilateral symmetrical signal changes (Figs.5a & 5b). On the other hand juvenile onset Krabbes leukodystrophy shows involvement of parieto-occipital white matter and pyramidal tract (Figs.5c & 5d). Diffuse cerebral atrophy is a feature of gray matter diseases such as neuronal ceroid lipofuscinosis (Fig.6a-d). MRI findings differs in infantile (Figs.6a and b) and juvenile onset neuronal ceroid lipofuscinosis (Figs.6c and d). Basal ganglia involvement is seen mainly in organic acidurias and mitochondrial disorders (Fig.7a). Brainstem involvement is mainly seen in mitochondrial disorders (Figs.7b and c) and Wilson's disease.

A definitive diagnosis of neurometabolic disorders



4a 4b

Fig.4. Metachromatic leukodystrophy – MRI: T2 weighted axial view - bilateral symmetrical white matter signal changes.

4a & 4b. The spared hypointense radially oriented white matter and dots within the hyperintense white matter may resemble the skin of tiger (radial stripes) and leopard (dots).

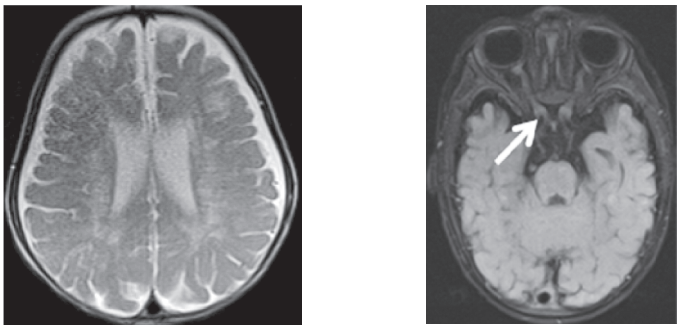


Fig.5a & b. Krabbe leukodystrophy – MRI: bilateral symmetrical signal changes and optic nerve hypertrophy (white arrow) in infantile onset disease

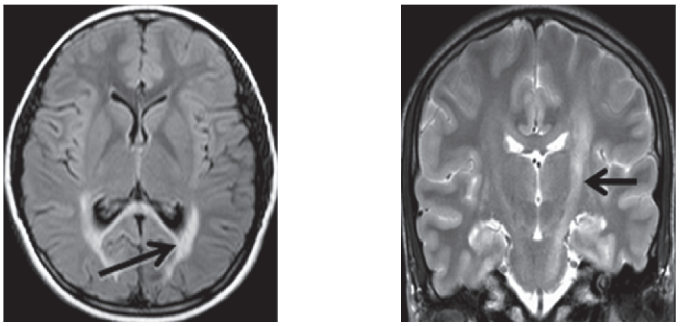


Fig.5c & d. Krabbe leukodystrophy – MRI: dominant parieto-occipital and pyramidal tract involvement (black arrows) in juvenile onset disease

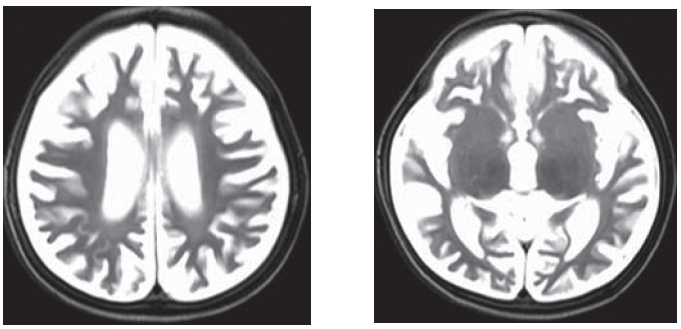


Fig.6a & b. Neuronal ceroid lipofuscinosis - MRI: severe cerebral atrophy in infantile onset NCL.

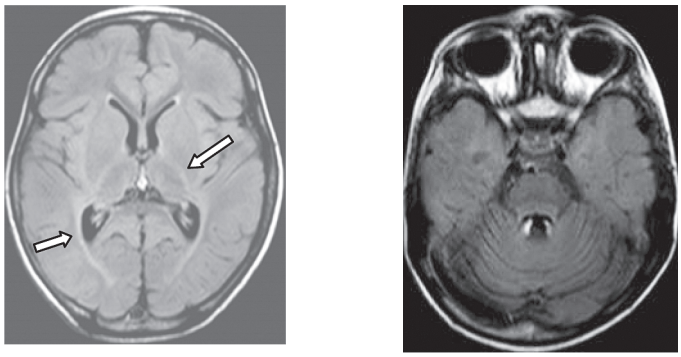
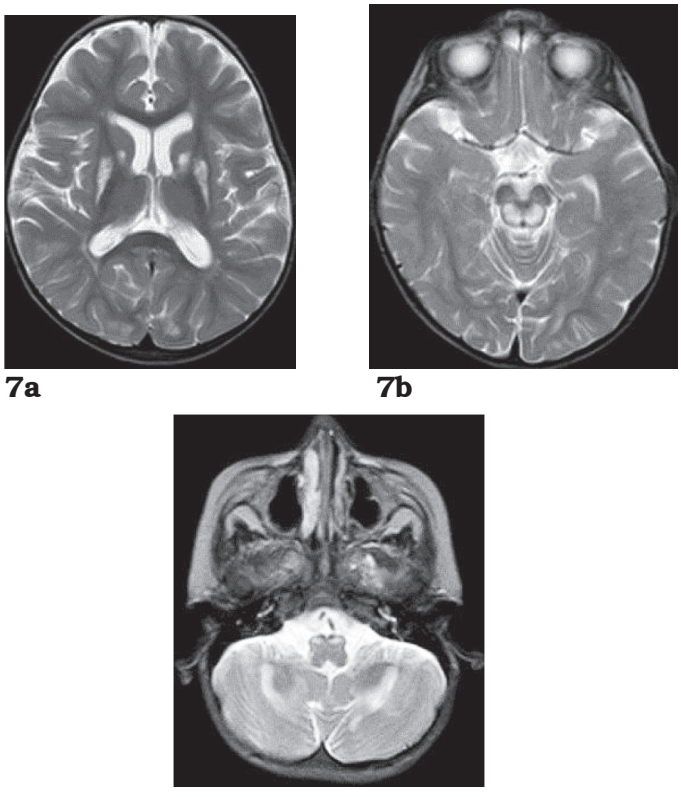


Fig.6c & d. Juvenile onset NCL - mild cerebellar atrophy with white matter signal changes in the periventricular white matter and posterior limb of internal capsule (arrows).



7a **7b**

7c

Fig.7. Leigh disease – MRI: bilateral symmetrical signal changes in basal ganglia (7a), dorsal midbrain (7b), inferior olivary nucleus &cerebellar white matter (7c)

requires access to specialized clinical biochemical and molecular genetic laboratories. A strong presumptive diagnosis is possible by quantitative analysis of the specific metabolites in certain small molecule disorders such as aminoacidopathies and organic acidurias. On the other hand the definitive diagnosis of organelle disease requires demonstration of enzyme deficiency. The assays are reliable when they are done on tissues such as peripheral blood leukocytes, cultured skin fibroblasts or in parenchymatous tissue obtained by biopsy.

The most specific form of diagnostic testing is by specific mutational analysis. With the advent of next generation sequencing it is easy to do sequencing of large number of genes implicated in metabolic diseases at a time. It is envisaged that screening is done by whole exome sequencing first followed by biochemical confirmation.[31] However, it is emphasized that clincial history and examination findings remain the key factors in interpretation of genomic data.[15]

Management

The rational treatment of metabolic disorders depends on the pathophysiological process responsible for the disease. In general the principles include the following steps:

1. Reduction of substrate load into the metabolic pathway by dietary restriction e.g. phenyl ketonuria, maple syrup urine disease/inhibition of enzymes in the metabolic pathway proximal to metabolic block (e.g. inhibition of synthesis of glycosphingolipids by miglustat an orally active iminosugar in Gauchers' disease)
2. Correction of product deficiency by substitution of deficient product (e.g. glucose supplementation in glycogen storage disorder by frequent feeding, nocturnal nasogastric drips in infancy), increasing the load of substrate and supplementation of alternate substrate (e.g. medium chain triglycerides in long chain fatty acid oxidation disorder and carnitine cycle defects)
3. Lowering toxic metabolite by its removal and blocking toxic effects (e.g. hemodialysis, exchange transfusion and peritoneal dialysis in case of hyperammoninemia)
4. Stimulation of residual activity by treatment with co-enzymes (e.g. biotin in biotinidase deficiency, riboflavin in glutaric aciduria Type 1 and thiamine in MSUD) and pharmacological chaperons (e.g.Fabry's disease, Gaucher's disease)
5. Supplying deficient enzymes by bone marrow transplantation (e.g.Mucopolysacharidoses), organ transplantation (e.g., liver transplantation in glycogen storage disorders, urea cycle disorder and organic aciduria), enzyme replacement therapy (e.g., Gaucher's disease, Fabry disease, Pompe disease) and gene therapy.

Conclusion

The advancement in genetics and metabolic disorders during the past few years have improved the diagnostic evaluation in children with metabolic disorders. Tandem mass spectrometry-based new born screening is a powerful screening tool and helps in early detection and treatment of these disorders and reduces morbidity and mortality. However, lack of facilities for specialized metabolic and genetic testing, expertise in proper interpretation of the results and management and the cost involved are major hurdles. Neverthless, there are a few conditions which can be treated or at least ameliorated by medical therapies and it is the physician's responsibility to identify them early. In addition, an etiological diagnosis shall help in relieving parents of anxiety and uncertainty and help them to join support and research networks. It also helps to limit the extensive testing which may be costly and invasive. From the physician's point of view a precise diagnosis helps in anticipating and managing associated medical and behavioural comorbidites, counseling regarding recurrence risks and preventing the additional familial burden through carrier identification and prenatal testing. Even when disease specific treatments are not available, the clinician can be of great help in maintaining the quality of life of both the child and the parents.

Points to Remember

- ***Neurometabolic disorders cause diverse neurological manifestations.***
- ***A systematic approach encompassing clinical, biochemical and magnetic resonance imaging helps in diagnosis.***
- ***It is important to be familiar with the age-dependent manifestations of the common neurometabolic disorders.***
- ***The rational treatment of metabolic disorders requires understanding of the pathophysiological process responsible for the disease.***
- ***Early intervention can improve the quality of life and prevent irreversible brain damage.***

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CLIPPINGS

Role of non-operative management in pediatric appendicitis.

Appendectomy is currently considered the standard of care for children with acute appendicitis. Although commonly performed and considered a safe procedure, appendectomy is not without complications. Non-operative management has a role in the treatment of both uncomplicated and complicated appendicitis. In uncomplicated appendicitis, initial non-operative management appears to be safe, with an approximate 1-year success rate of 75%. Compared to surgery, non-operative management is associated with less disability and lower costs, with no increase in the rate of complicated appendicitis. In patients with complicated appendicitis, initial non-operative management with interval appendectomy has been shown to be safe with reported success rates between 66-95%. Several studies suggest that initial non-operative management with interval appendectomy may be beneficial in patients with perforated appendicitis with a well-formed abscess or inflammatory mass. Recent data suggest that interval appendectomy may not be necessary after initial non-operative management of complicated appendicitis.

Dani O. Gonzalez, Katherine J. Deans, Peter C. Minneci. Role of non-operative management in pediatric appendicitis. Semin Pediatr Surg May 2016.

PEDIATRIC NEUROLOGY

TRAUMATIC BRAIN INJURY

***Soonu Udani**

Abstract: *Traumatic brain injury (TBI) is the most common cause of intracranial hypertension. The hallmark of TBI is cerebral edema and raised intracranial pressure with its detrimental effect on the brain. The focus here is on the practical aspects of controlling intracranial pressure, maintaining cerebral perfusion pressure and supporting the patient's hemodynamics and vital functions during the initial critical days.*

Keywords: *Traumatic brain injury, Intracranial pressure, Cerebral perfusion pressure, Neuromonitoring.*

In epidemiological data collected by Gururaj, it is estimated that nearly 1.5 to 2 million persons are injured and 1 million succumb to death every year in India. Road traffic injuries are the leading cause (60%) of TBIs followed by falls (20%-25%) and violence (10%). Alcohol involvement is known to be present among 15%-20% of TBIs at the time of injury.[1] Children are victims of adult negligence in most cases. Severe injury, known as severe TBI, enough to warrant therapy for increased intracranial pressure (ICP), occurs in less than 10% of cases.

In head trauma, focal damage due to direct tissue injury and diffuse injury due to acceleration or deceleration results in hemorrhage, cerebral edema and diffuse axonal injury. TBI occurs in two phases: primary injury, which is the tissue or mechanical damage at trauma and secondary injury, caused by inflammatory and excitotoxic cytokine release, leading to edema and elevated ICP.[2] Secondary injury can also partly, if not totally, be prevented, as it is caused by physiologic insults like hypoxemia, hypotension, hypo or hyperglycemia and hypo or hypercarbia. We can do little about the primary injury but secondary injury is preventable using ICP interventions, meticulous nursing care and other therapeutic interventions that begin from the time of recognition of injury.

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As most of the mortality and morbidity stems from increased ICP and its secondary damage, all management issues tend to be directed towards this factor. Keeping the brain well perfused for the crucial first week when ICP can remain high, is the main if not only goal of all therapy. Monitoring too, is designed to detect the earliest rise in ICP or the drop in perfusion to enable quick and appropriate therapeutic decisions to be made.

Primary brain injury

It varies from mild to severe, is not directly preventable and is of the following types:

- Concussion (short loss of normal brain function in response to a head injury) is not serious but can have sequelae-like headaches, behavioural changes and rarely seizures.
- Contusion (direct injury with neuronal damage) varies in severity with results depending on the extent and position. Small contusions in areas like the temporal lobe can cause early herniation.
- Diffuse axonal injury (DAI) may not be obvious on CT/MR at first and may need a repeat imaging. Later massive edema may result 24-72 from injury and can last up to 7-10 days. The prognosis is also variable and not necessarily as poor as was earlier thought.
- Subdural or extradural hematomas are surgically amenable to removal. Not every hematoma requires surgical intervention but all need close monitoring and repeat imaging at 24-48 hours.

Indications for repeat imaging are (i) any new neurological signs or symptoms, including vomiting, seizures, neurologic deficits or abnormal behavior, (ii) drop in Glasgow coma scale (GCS) of > 2 even if not below 9, (iii) hematomas, contusions seen on first CT and (iv) autonomic signs and or pupillary changes in sedated / paralysed patients (BP, HR, eye deviation, sweating, etc).

Examination and assessment needs to be as complete as possible with attention to pupils, deficits and the GCS (Table I). GCS also needs to be repeated at regular intervals for improvement or deterioration as vital decisions will depend on its accuracy. Hence written documentation in simple terms for all team members to follow is important.

Table I. Glasgow coma scale with pediatric modification

Criteria	Adult	Child	
Eye opening	Spontaneous	Spontaneous	4
	To command	To sound	3
	To pain	To pain	2
	None	None	1
Verbal response	Oriented	Age-appropriate verbalization, orients to sound, fixes and follows, social smile	5
	Confused	Cries, but consolable	4
	Disoriented	Irritable, uncooperative, aware of environment	3
	Inappropriate words	Irritable, persistent cries, inconsistently consolable	
	Incomprehensible sounds	Inconsolable crying, unaware of environment or parents, restless, agitated	2
	None	None	1
Motor response	Obeys commands	Obeys commands, spontaneous movement	6
	Localizes pain	Localizes pain	5
	Withdraws	Withdraws	4
	Abnormal flexion to pain	Abnormal flexion to pain	3
	Abnormal extension	Abnormal extension	2
	None	None	1
Best total score			15

(Usually a score of <12 corresponds to "coma". Children less than 2 years of age should receive full verbal score for crying after stimulation)

Treatment for severe head trauma starts immediately as the patient is recognized to be having or being at risk for increased ICP. A stepwise approach to control of ICP is advocated in three tiers, with escalating levels of care.

Safe transport: Children should be transported on proper stretchers by ambulance and not in cars and other vehicles unless absolutely unavoidable. The facility chosen needs to have the ability to handle imaging, intensive care and surgical intervention under one roof, or re-transport will become necessary.

Indications for CT Scan

The NICE guidelines has laid down the following criteria (Table II).[3]

Airway management

A child with a GCS score of ≤9 or a waxing and waning mental status should have a definitive airway for controlled ventilation and airway protection (Box 1). The chin lift and jaw thrust maneuvers can be safely performed if correctly done, to open the airway without hyperextending the neck or risking cervical cord injury. If unsure of the technique, only the jaw thrust should be used. Oral airways may irritate and increase ICP and should be used with caution in an unconscious patient. Nasal airways are contraindicated in facial trauma. Video/ bronchoscopic assisted intubation may be required by an expert in difficult situations. Cervical spine stability must be ensured with a collar or in-line stabilization.

Table II. Criteria for CT brain in TBI

Immediate CT brain indications:
Suspicion of non-accidental injury
Seizure after injury in non-epileptic
GCS < 14 on arrival or < 15 after 2 hours of injury
Focal signs
Depressed fracture / open fracture / tense fontanelle
Laceration more than 5 cm in less than 1 year age
Combination with the above or signs that may appear alone at any time, warranting a CT scan:
Witnessed loss of consciousness more than 5 minutes
Abnormal drowsiness
More than 3 vomiting episodes
More than 5 minutes amnesia
Dangerous level of injury- high speed collision. [Liddel's triad (head, leg, abdomen)]
The threshold for scanning should be lower if the child is known to have a bleeding disorder or is on any type of anti coagulant or anti platelet agent.
Cervical spine imaging:
1. Dangerous level of injury- high speed collision. [Liddel's triad (head, leg, abdomen)]
2. Paraesthesias
3. Focal deficit
4. Abnormal respiratory pattern / respiratory distress not attributable to central causes
5. Inability to apply clinical examination and voluntary neck flexion to check for pain and restriction due to non-cooperation or coma
(There is a high degree of error in the reading of any modality of cervical spine imaging and a radiologist must give an opinion on the study before the spine is considered 'cleared').

The recommended approach to establishing an airway is to administer pre-oxygenation with tidal breathing for three minutes, induce anesthesia including muscle relaxation, perform direct laryngoscopy, and orotracheal intubation with gentle cricoid pressure, using in-line cervical stabilization.

Sedation and analgesia

Once intubated, the child needs to be well sedated with good analgesia. The mistaken belief that deep coma requires no sedation and the person feels no pain has now been relegated to history. All sedative and hypnotic agents that are commonly used like thiopental, propofol and etomidate[4]are potent cerebral vasoconstrictors and lead to a reduction in cerebral blood flow as well as cerebral metabolic rate of oxygen consumption ($CMRO_2$), which leads to decreased ICP. They therefore have an important role in preventing or limiting secondary brain injury and intracranial hypertension by reducing cerebral metabolic rate and attenuating undesired stress responses, such as from pain, shivering, anxiety and discomfort. Because of the anticonvulsant actions of some of them, they are useful in infusion form in the post intubation period. However, the use of these agents needs a degree of hemodynamic

Box 1. Indications for tracheal intubation

- Loss of pharyngeal reflexes- Risk of aspiration
- Apnea
- Cervical spine injury
- GCS ≤9
- Decrease in GCS by > 2 irrespective of previous GCS
- Anisocoria
- Hypercarbia $PaCO_2$ >45 mmHg
- Hypoventilation from neuromuscular disease
- Need to control ventilation-even when the patient is hyperventilating- $PaCO_2$ <25 mmHg

stability as the BP may fall as they cause peripheral vasodilatation and vasoplegia and hence support with vasopressors often becomes necessary to maintain BP.[5]

General measures: In the eagerness to employ high-end technology driven monitoring and neurointensive care, good and sound nursing practice and time tested Tier I therapy should not be neglected.

Tier I therapy

General care: As the child needs to be cared for in extremely controlled and well monitored conditions, with the gentlest of handling, good, protocolized nursing care is crucial.

1. 30° head up unless shock is present
2. Hourly pupil and GCS check and recording
3. Eye care with lubricant and closure to prevent exposure keratitis
4. H2 blockers to prevent stress ulcers
5. Bladder care and bowel care to prevent pain and constipation
6. Suctioning with premedication with IV/and or ET lignocaine
7. Prevention and prompt treatment of fever
8. Seizure prophylaxis and prompt recognition of seizures to further prevent rises in ICP
9. Preventing bed sore and other pain check as pain will raise ICP
10. Watching for development of autonomic dysfunction: sweating, tachy/bradycardia, anisocoria.
11. Monitoring for swings in BP and temperature in concurrent spinal injury, status epilepticus
12. Deep vein thrombosis (DVT) prevention in over weight and obese children.

Basic monitoring

Hourly Glasgow Coma Scale charting appropriate for age is important as a drop of two points, even if not below 8, is an indication to step up therapy and endotracheal intubation of the child. Heart rate, arterial blood pressure (ABP), autonomic response and pupillary response should be monitored as they may herald seizures, raised ICP or reduced CPP and or herniation.

ABP: Invasive arterial blood pressure monitoring is important for both, continuous blood pressure monitoring and for blood sampling to reduce pain. Without ABP it is not possible to calculate cerebral perfusion pressure (CPP) even if the ICP monitor is in place.

Central venous pressure (CVP): CVP monitoring is more useful for drug delivery than for assessing intravascular volume status as hypertonic agents and many vasopressors cannot be given via a peripheral line.

Urine output must be monitored in the child with significant TBI as electrolyte abnormalities due to diabetes insipidus or syndrome of inappropriate antidiuretic hormone may be present.

Osmotherapy

This would be the first line of therapy when GCS is less than or equal to 12. If the child is drowsy give osmotherapy even if GCS is more than 12 (Box 2).

Box 2. Treatment based on GCS

If GCS >12 but drowsy ! initial trial of hyperosmolar agents

If GCS ≤9 or any s/o herniation, ! sedate, paralyze, intubate and ventilate

If GCS 10-12 watch neurological signs, vitals and pupils carefully and hourly

Hypertonic saline: 3% - 7.5% saline is replacing mannitol as the first line hyperosmolar agent. In 3% saline use, doses for bolus therapy range from 5 to 10 ml/kg.[6] Contrary to earlier belief that sodium levels should be allowed to rise, Na levels ranging between 155-160 mMol/L is preferred nowadays. In a recent study, children with sustained (>72 hours) serum sodium levels above 170 mEq/L had a significantly higher occurrence of thrombocytopenia, renal

failure, neutropenia and acute respiratory distress syndrome.[7] Hyperchloremic acidosis is another often encountered problem whose clinical significance is uncertain.

Mannitol: There is limited clinical evidence to support the use of mannitol for the treatment of ICP, except its traditional use. Potential complications include natriuresis and dehydration, possible concern for acute renal failure and a rebound edema, where the accumulation of mannitol in the tissue causes movement of water back into the brain parenchyma, possibly increasing ICP. The practice of using mannitol at regular intervals arbitrarily for several days is not acceptable for the very complications mentioned.

Controlled ventilation: Controlled ventilation is preferred to prevent the risk of cerebral ischemia. Regional cerebral blood flow (CBF) and oxygen consumption have been measured at three levels of arterial CO_2 (>35 mmHg, 25-35 mmHg, and <25 mmHg), and it was found that regional ischemia occurred in 28.9% during normocapnia and increased to 59.4% with $PaCO_2$ 25-35 mmHg, and 73.1% for $PaCO_2$ less than 25 mmHg, indicating the increasing risk of cerebral ischemia associated with hyperventilation.[8]

The principles of ventilation are:

1. Provide uniform ventilation with adequate and fixed tidal volume (VT) or 'controlled ventilation' so as to have the least fluctuations in $PaCO_2$ levels
2. VT should be kept at 8 ml/kg to prevent atelectasis.
3. End-tidal CO_2 reduces the need for frequent blood gases after initial correlation.
4. PaO_2 kept always > 60 mm Hg, No change in CBF till PaO_2 reaches 60 mm Hg below which the CBF rises steeply causing ICP to rise.
5. CO_2 must be kept in the range of 35-40 mmHg to prevent brain ischemia. There is an almost linear relationship with $PaCO_2$ levels and CBF. It is the change in pH that induces vasoconstriction or dilatation affecting CBF and therefore ICP.
6. PEEP levels should be kept below 8 as far as possible unless the lung condition and severe hypoxemia warrants otherwise (ICP monitoring helps here to titrate PEEP).
7. Central neurogenic hyperventilation may need to be overcome by sedation and paralysis to prevent the vasoconstricting effects of hypocapnia.
8. Endotracheal suctioning should be done only when required and preceded by lignocaine 1-2 mg/kg iv/ intratracheal 2 minutes prior.
9. 30-25 torr CO_2 for short periods of <15 minutes may be employed. Autoregulation may be lost if used for prolonged periods.
10. The merits and demerits of hyperventilation should be kept in mind (Table II).

Table II. Hyperventilation - Merits and demerits

Merits	Demerits
Restores pH	Cerebral ischemia
Improves autoregulation	Hypoxia- focal/global
Decreases ICP	Local inverse steal
Increases CPP	More adverse effects

Fluids and nutrition: Fluid restriction is not required unless the syndrome of inappropriate anti-diuretic hormone (SIADH) sets in. This is unusual on initial presentation and is usually seen after day 2. Isotonic, non-glucose containing fluids at the maintenance for age are to be started and euglycemia to be maintained. Hyperglycemia is associated with poor outcome and increased lactate formation in the brain and a level of less than 150-180 mg/dl should be the aim.[9] After the first 24 hours, glucose can be added to the IV fluids or better yet, enteral nutrition started.

Seizure prophylaxis: The current standard is that patients should be placed prophylactically on an antiepileptic drug (AED) for the first 7 days. If patients do not experience seizures, it is recommended that they be weaned off the AED. This is based on two facts: 1) there is a significantly lower occurrence of short-term seizures in patients placed on phenytoin (PHT) versus placebo and 2) whether these patients are weaned off AED or remain on it, their long-term outcome for remote symptomatic epilepsy or post-traumatic epilepsy is unchanged.

Phenytoin alters other drug metabolism, causes fever and requires therapeutic-level monitoring. Levetiracetam does not require serum monitoring or have significant drug interactions and can be safely used in organ failure.

A large trial of two arms was done between two centres where phenytoin was used in one centre and levetiracetam at the other in 406 vs 407 patients of head trauma and there appeared to be no difference in the results of the two arms in the data shown.[10]

Levetiracetam is as effective as phenytoin in preventing early post-traumatic seizures but is associated

with an increased seizure tendency on EEG analysis in a study by Jones et al.[11] However, this was an extremely small study and needs revalidation but now exists a greater tilt towards levetiracetam due to its safety profile and equal efficacy.[12]

Tier II therapy

This is started when the simple measures to control ICP appear to be inadequate and the child shows either clinical or radiological deterioration. They are undertaken after a meticulous check of all the previous steps to ensure that adequate control of all mitigating factors has been achieved. These steps include:

ICP monitoring

Barbiturate coma

Intermittent hyperventilation

Controlled hypothermia (may be considered in tier III)

ICP and cerebral perfusion pressure (CPP)

CPP is the pressure at which the brain will be perfused and maintain its integrity. Hence it appears logical that therapeutic measure should be aimed at maintaining CPP as in shock we would try to maintain mean arterial pressure (MAP). CPP = MAP-ICP.

So higher the ICP lower would be the CPP. Cerebral autoregulation may be locally or globally disrupted when the brain is injured. As CPP is determined by the difference between MAP and ICP, hemodynamic support to maintain MAP and CPP is critical in TBI in order to prevent secondary injury. When autoregulation is intact, CPP and CBF is maintained constant at a range of MAP of 50-150 mmHg. When there is impaired autoregulation and systolic blood pressure less than the 5th percentile, especially in the first 6 hours, there is a high risk of poor long term outcome. These are independent risk factors for all levels and types of injuries. Hence the stress on maintaining good hemodynamics right from the time injury is recognized.

The exact optimal CPP in the pediatric patients is unknown, and there are numerous studies included in the 2012 Guidelines.[13] In a report of 188 head-injured children with ICP monitoring, no patient with a CPP less than 40 mmHg for more than 4 hours survived. The exact relationship between age and optimal CPP is unknown. In the absence of ICP monitoring and suspected elevated ICP, systemic mean arterial blood pressure should not be allowed to decrease below values normal for age. Maintaining CPP > 50 mm Hg in 6- to 17-year-olds and >40 mmHg in 0- to 5-year-olds are appropriate targets (Box 3). This would mean specific attention to blood pressure. Maintaining age-appropriate systolic blood pressure (SBP) greater or equal to the 75th percentile may also be associated with better outcome.[14]

Box 3. Targeted CPP

CPP = MAP-ICP is an important equation that needs to be remembered. Most therapies are focused on preventing rises in ICP and keeping MAP normal or high normal so that CPP stays in the range of:

40-50 mm Hg for infants

50-60 mm Hg for children

>60mm Hg for > 12 yrs

ICP should be treated when it exceeds 20-25 mm Hg. Without monitoring, this value would be impossible to determine. Clinical signs appear well after the ICP has risen and treatment could well be delayed. The presence of coagulopathy would contraindicate the placement of an ICP monitor, in which situation the Cushing reflex and autonomic dysfunction and pupillary changes may be the only indicators of increased ICP or impending herniation.

Monitoring of ICP is a level II recommendation for patients with a GCS $\leq$ 8 with an abnormal CT scan or Level III recommendation with a normal scan but with posturing or unequal pupils.

An intraventricular catheter would have the added advantage of allowing for CSF drainage when ICP rises but is more difficult to insert and may get blocked with blood.

Under rare conditions, when an intraventricular catheter is in place for supratentorial CSF drainage and ICP is being monitored, a lumbar drain may be placed for lumbar drainage of CSF. This is not to be undertaken in inexperienced hands or when there is a unilateral lesion as the danger of over-drainage and herniation is very real.

The intraparenchymal catheter is expensive but easier to use and does not require recalibration often. Both catheters have the ability to display the waveform (Fig.1).

Advanced neuromonitoring

This includes cerebral micro-dialysis, transcranial Doppler (TCD), thermal diffusion probes, near-infrared spectroscopy (NIRS), and jugular oximetry. The evidence for these monitors in TBI is limited with little evidence showing how these can change mortality or guide therapy.

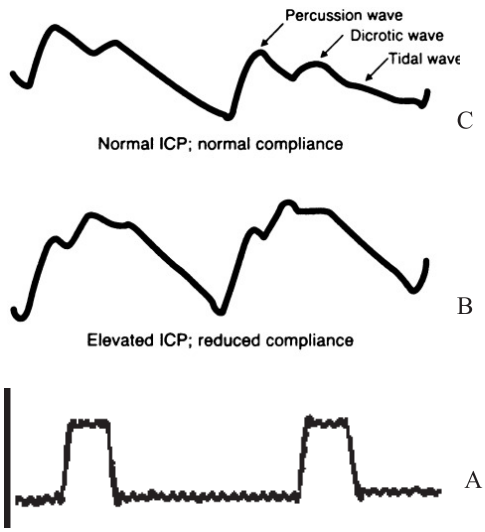

Fig 1. ICP wave forms

1. Compliant brain resembles arterial waveform C waves
2. Non-compliant brain: dicrotic notch rises B & A waves

   Lundberg C waves have an amplitude up to 20 mmHg and a frequency of 4-8 per minute, and may be seen in the normal ICP waveform.

   Lundberg B waves are shorter duration (minutes) increases of ICP to 20-50 mmHg, but may progress to A waves.

   Lundberg A waves or plateaus are characterized by increase in ICP to 20–100 mmHg with a duration of minutes to hours, and may indicate risk of low CBF.

The 2012 Guidelines[13] recommend maintaining cerebral brain tissue oxygenation (PbtO2) at ≥ 10 mmHg, based on level III evidence of brain oxygenation monitoring.[15]

Barbiturate therapy: When tier one therapy fails to reduce ICP the presumption is that the situation is grim and the child faces death or severe disability from brain damage. Barbiturates reduce the cerebral metabolic rate and consumption of oxygen and reduce ICP. However, the flip side of the coin is that they can cause hypotension and hemodynamic instability which will reduce CPP and injure the brain further. Vasopressor support may be needed. Hence, this level of therapy needs high level care and full monitoring capabilities. As the ICP is high, the MAP needs to be maintained above the 75th if not the 90th percentile and this can be an uphill task in the face of vasodilatation and vasoplegia caused by these drugs. Vasopressors that have little or no effect on the heart but have more systemic vascular resistance (SVR) raising properties, like noradrenaline or phenylephrine are recommended. Dose is always titrated to effect or side effects. There is also current data on the use of vasopressin for organ preservation or profound hypotension.

Thiopental with a loading dose of 2-5 mg/kg, followed by an infusion of 1-2 mg/kg/hr titrated upto a burst suppression on the electroencephalograph (EEG) or dose limiting side effects can be started. Prolonged infusions can result in serious myocardial depression.

Continuous EEG monitoring is also an important tool at this stage. Acute symptomatic seizures after TBI especially, can go unrecognized in the sedated ventilated patients and have a poor prognosis as compared to remote symptomatic seizures. Prompt treatment can only be given if recognition by continuous EEG monitoring is on.[16]

Hypothermia (Core body temperature of <35^{o}C): Reducing the temperature of the brain reduces its metabolic rate, consumption of oxygen, propensity to seizures and increased ICP. Hence logically it would be an ideal way to control ICP. Head cooling is possible in the thin neonatal skull. Beyond that age, whole body cooling becomes essential to prevent uneven cooling and rewarming. Moderate hypothermia (32-33°C) is what has been studied and practised. Even this should be reserved for refractory ICP and especially in a fully equipped and well staffed PICU in a tertiary care.

All patients need ICP, arterial BP, CVP and frequent if not continuous EEG monitoring. Cardiac arrhythmias are often seen in seriously head injured patients and it may be difficult to separate those occurring from interventions and those from the brain injury. In one study, 5/7 patients in the hypothermia group and 2/9 in the normothermia group developed arrhythmias.[17] The clinical impact of these was unclear. Other complications of hypothermia include dyselectrolytemia, disseminated intravascular coagulation (DIC), sepsis, gut ischemia and skin breakdown. In the study led by the Adelson group, there were 21% deaths in the hypothermia group and 12% in the normothermia group.[18] The need for vasoactive agents was seen to be higher too, especially during the rewarming period. This is the consensus statement in the document: "In the final analysis, hypothermia is not recommended as a primary modality for neuroprotection due to the possibility of increased mortality. However, when faced with refractory ICP, the inherent risks could be acceptable when offset against the high risks of threat to life and severe disability that high ICP causes".

Decompressive craniectomy: When medical measure fail and there is a serious risk of death or disability as weighed

against the risk of surgical intervention, bilateral or unilateral temporo-pareital decompression of the cranial vault is offered. This allows space for the brain to expand in the face of increasing pressure and takes off pressure of the squeezed neurons, improving CPP. The timing needs to be correct as it would be in vain if there is already neuronal death from a prolonged high ICP with a very low CPP of less than 40 mm Hg with poor chance of recovery. There is obviously no perfect time and it is a clinical call.

A stepwise approach with appropriate timing, some being done simultaneously, is given in Box. 4.[19]

Box 4. Columbia Stepwise Protocol

- Surgical decompression of hematoma/s
- Sedation and analgesia
- CPP optimization
- Osmotherapy
- Hyperventilation
- Barbiturates
- Hypothermia
- Decompressive craniectomy

Recovery and prognosis: Recovery is a dynamic process. The initial phase of recovery from the acute life threatening period of raised ICP gives way to a period of waiting and rehabilitation that needs patience and perseverance. The more severe the head injury the worse the outcome and the severity an early predictor of mortality and morbidity seems obvious. In a study of 315 patients with GCS of equal to or <8, the model which provided the most accurate prediction of poor outcome included age, hypotension and three different CT characteristics, subarachnoid blood, intra cerebral hematoma or intracerebral contusion (accuracy 72.5%).[20] The Glasgow outcome scale-extended (Pediatrics) is one long term rating scale that is used to judge long term results of head injury. The 8 categories are: Dead, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery and upper good recovery. A structured interview has been provided to improve reliability of rating.[21,22]

Magnetic resonance imaging may be more useful as a predictor of long term outcome at discharge from hospital. Whole brain volume and total brain grey matter is reduced, and total ventricular volume, total CSF volume, and ventricle-to-brain ratio (VBR) are increased in the TBI group. Volumetric measures of preserved fronto-temporal tissue is related to functional recovery as measured by the Glasgow Outcome Scale (Pediatrics) with greater tissue preservation predicting better recovery.[23]

In the final analysis, we need to be quick, meticulous and focused in treating these children with a keen eye on neuronal preservation. While many research tools may be in the pipeline, what is available to us is good clinical practice that we can adhere to within the framework of our working conditions. The steps outlined here are within universal guidelines to guide therapy.

Points to Remember

- ***Basic monitoring and meticulous care is of prime importance in the management of traumatic brain injury.***
- ***Seizures, fever, pain and sedation need close attention.***
- ***CPP targeted therapies hold promise for better outcomes.***
- ***ICP monitoring is useful for targeting therapy.***
- ***Hypertonic saline is preferred over mannitol.***
- ***Hypothermia is advised only in refractory life threatening ICP.***
- ***Attention not only to mortality but also to good outcome is vital.***

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NEWS AND NOTES

IV Workshop on "Clinical Evaluation in Pediatric Neurology"

Kalawati Saran Children's Hospital

Date: 6th & 7th August, 2016

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PEDIATRIC NEUROLOGY

HYPOXIC ISCHEMIC ENCEPHALOPATHY IN CHILDREN: AN INTENSIVIST'S PERSPECTIVE

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Abstract: *Hypoxic ischemic encephalopathy is a syndrome of acute global neuronal injury resulting from combination of hypoxia, ischemia and reperfusion. The clinical conditions leading to HIE in children include cardiac arrest, asphyxia and drowning. Anatomical areas of the brain vulnerable to hypoxia and ischemia include hippocampus, caudate and putamen with relative sparing of the brainstem. The most common clinical presentation is altered consciousness. The key objective of intensive care management is to anticipate, prevent and treat secondary physiological insults to the brain through a structured protocolized 'neuroprotective approach'. Therapeutic hypothermia is coming up as an option for older children especially in out-of-hospital cardiac arrest once return of spontaneous circulation is achieved. Outcome goals are quality survival rather than survival alone.*

Keywords: *Hypoxic ischemic encephalopathy, Children, Intensive care, Neuroprotection.*

Hypoxic ischemic encephalopathy (HIE) is a major cause of morbidity and mortality in critically ill children requiring intensive care. HIE imposes a heavy burden not only for the patient, in terms of disability and quality of life but also for healthcare systems in terms of high costs. Hypoxic-ischemic brain injury comprises of a constellation of pathophysiological and molecular injuries of the brain induced by combination of hypoxia, ischemia and cytotoxicity.[1] Reperfusion aggravates the primary insult manifesting clinically as hypoxic ischemic encephalopathy. Varied etiologies in children can culminate into this common final pathway. The management and prognosis of HIE is determined by developmental stage of brain and timing of the insult, regional vulnerability and etiology, thus explaining why similar degree of insults can have different repercussions in newborns, infants and children.

Irrespective of the primary trigger, the quality of life in survivors is mainly determined by the degree of neurological recovery. Thus, the thrust is more on quality of survival rather than survival alone. To achieve this goal there is a pressing need for a multidisciplinary team along with specialized equipment to provide high quality neurocritical care. The key objective of such an intensive care team is to anticipate, prevent and treat secondary physiological insults to the brain. This 'neuroprotective strategy' hinges on a structured protocolized approach that focuses chiefly on preventing cerebral hypoxia, ischemia and avoidance of raised intracranial pressure, systemic hypoxia, hypotension, hypocarbia and hypoglycemia. In short, it is a tight rope balancing act in which the cerebral and systemic targets are to be maintained diligently.

Pathophysiology[2]

The key initiating trigger in HIE is the lack of oxygen and glucose that leads to global brain injury. Hypoxia leads to decrease in ATP production through aerobic pathway thus resulting in energy failure and loss of neuronal cell integrity. Increased release of excitotoxic amino acids (glutamate, glycine) due to membrane failure coupled with their decreased uptake causes brain injury via NMDA receptors. NMDA-mediated glutamate excitotoxicity causes an intracellular calcium influx that activates the secondary messengers amplifying the cellular injury by increasing calcium permeability and glutamate release thus creating a vicious cycle. The above chain of events also results in the activation of neuronal nitric oxide (NO) synthase and consequent generation of oxygen free radical species. The latter are responsible for cellular injury by direct DNA fragmentation, protein oxidation, lipid peroxidation and disruption of the mitochondrial respiratory chain with initiation of cell death cascades. The three pathways - necrotic, apoptotic and autophagic ultimately lead to neuronal and glial cell death.

Cardiac arrest in children

Cardiac arrest is an important cause for HIE in children, which may occur out of hospital (OHCA) or in

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hospital (IHCA) or due to other causes like drowning, strangulation, stroke, etc. Cardiac arrest due to asphyxia is the most common cause of global HIE in infants and children. Cardiac arrests in children generally result from respiratory failure, circulatory shock, or both leading to pulseless electrical activity (PEA) and ultimately asystole. Nadkarni, et al in their prospective observational study, observed that the first documented pulseless arrest rhythm was typically asystole or PEA in both children and adults.[3] More than 50 % of survivors develop some degree of HIE with multiple neurological disabilities which evolves after insult. Recent data from a tertiary centre showed that the incidence of in-hospital CPR for all hospital admissions (n=4654) was 6.7% (n=314) of which 64.6% (n=203) achieved return of spontaneous circulation (ROSC), 14% (n=44) survived to hospital discharge and 11.1 % (n=35) survived at 1 year.[4]

The cerebral blood flow (CBF) pattern studied during post cardiac arrest phase in adult animal models can be divided into four phases

1. **Phase I**: Multifocal (regional) no-reflow
2. **Phase II**: Hyperemia (15-30 minutes after ROSC)
3. **Phase III**: Delayed hypoperfusion (begins approx after 30 mins of ROSC may last for hours)
4. **Phase IV**: Restoration of normal blood flow

In the setting of pediatric asphyxial cardiac arrest, with progressively increased insult duration, the phase II is diminished in intensity in all regions with phase III predominating at long insult durations.[5]

Clinical features of HIE

The clinical manifestations of HIE depend on its severity. Though effects of hypoxia and ischemia predominate in the central nervous system, other organ systems like cardiac, respiratory and renal can also be affected. The manifestations can be both early and late. High anticipation and early recognition is the key for achieving better outcomes.

Central nervous system: Altered consciousness is a salient feature of HIE as neurons involved in consciousness and arousal are prone to hypoxic damage. The areas/neurons that are selectively vulnerable to hypoxic/ischemic injury and their corresponding clinical manifestations[6,7] are as given in Table I.

The brainstem is relatively spared in HIE. Post-ischemic seizures can be convulsive or non-convulsive and are caused by excessive excitatory transmitter release that commences within minutes and lasts several hours post HIE. Delayed and difficult to control anoxic myoclonic seizures may occur within 24-48 hours of HIE. Movement disorders due to basal ganglia and cerebellar damage are usually a delayed manifestation of HIE.

Cardiovascular system: Myocardial dysfunction, especially left ventricular dysfunction secondary to ischemia and reperfusion injury usually manifests as cardiogenic shock. These children are also at high risk for arrhythmia.

Respiratory system: Respiratory problems encountered in HIE range from loss of airway reflexes and respiratory

Table I. Vulnerable areas and manifestations in HIE

Areas affected	Manifestations
Basal ganglia, putamen, caudate	Dystonia, impairment in attention, memory, chorea
Globus pallidus	Akinetic, rigid syndrome
Cortex (layers 3 &5)	Coma, persistent vegetative state, seizures, myoclonus and language impairment.
Watershed areas ACA-MCA MCA-PCA	 Brachial diplegia Cortical blindness
Cerebellum	Dysmetria, fine movement disorder
Hippocampus (CA1 region)	Seizures, amnesia, memory deficit

drive to severe ARDS. Some children may have ventilator dependence with need for tracheostomy.

Gastrointestinal system: There may be bowel ischemia with altered aspirates and lactic acidosis, rarely perforation. Hypoxic hepatitis which when seen with HIE carries a high mortality.

The other systems involved can be renal, endocrine and hematological. Post-HIE acute kidney injury with or without tubular necrosis may be seen. Dysglycemias may occur due to alterations in ADH, cortisol, ACTH, insulin and glucagon levels. Hematologic and coagulation disorders though not well described may also be seen.

Management of patients with HIE

Supportive management of patients with HIE is similar irrespective of the etiology. The key objective of intensive care management of post cardiac arrest patients is prevention of secondary insults. Stabilization and maintenance of ABC's after return of ROSC is vital; airway should be secured with endotracheal intubation and mechanical ventilation should be instituted. All children require continuous cardiorespiratory monitoring, and gastric decompression with an orogastric tube. Urinary catheterization is required for close monitoring of urinary output. Stress ulcer prophylaxis is generally to be given for all. It is important to have adequate peripheral venous access in all and central line in those requiring vasoactive infusions. After initial stabilization, it is useful to perform a quick neurologic assessment of the patient. Patients remain at significant risk of secondary brain injury after ROSC from hypotension, hypoxemia, seizures, hypoglycemia, and hyperthermia; so efforts should be made to prevent these conditions, or treat them promptly as they occur.[7]

Intracranial pressure management: Raised intracranial pressure is part and parcel of global hypoxia ischemia and can be severe enough to cause herniation syndrome especially if the period of ischemia is long drawn. Therefore it is prudent to start all children with HIE on first tier anti-raised ICP measures as given below:[8]

a) Head in neutral position with 30° elevation to promote venous drainage via the external jugular veins.

b) Minimum stimulation and adequate sedation and analgesia with midazolam 1-3 mg/kg/min and morphine 0.1 mg/kg/hr every 6 hourly titrated to achieve a Ramsay sedation scale score of 3-4.

c) Maintain normoxia (PaO_2> 60 mmHg, SpO_2> 92%), normocarbia (pCO_2 ~ 35 mmHg),

d) Maintain euvolemia and normal blood pressure (Mean arterial blood pressure >50th centile)

e) Fever should be strictly avoided.

f) Random blood glucose should be kept at around 150 mg/dL. Hypoglycemi (<60 mg/dL) and hyperglycemia (>180 mg/ dL) are to be avoided.

g) Stress ulcer prophylaxis should be instituted with either antacid 1 mL/kg/dose every 8 h or pantoprazole 1 mg/kg/dose every 12 h, the latter preferred in the presence of gastrointestinal bleed.

In children with signs of impending herniation (unequal pupils or posturing) short term hyperventilation (double the normal breathing rate for a given age) for 10 minutes should be immediately undertaken with a self-inflating bag targeting a PCO_2 of 30-32 mm Hg. Though the routine use of osmotherapy has not been very well studied in HIE, hypertonic saline or mannitol can be used for prevention of cerebral herniation. The former is given as 10 mL/kg loading followed by continuous infusion 0.1-1 mL/kg/hr targeting a sodium goal between 145-155 mEq/L and the latter is given as 0.5 g/kg bolus and repeated every 6 hourly in dose of 0.25 g/kg. The early effect (within 15-30 min) of mannitol is due to reduction in the blood viscosity and improved microvascular cerebral blood flow, whereas the late effect (last up to 6 hrs) results from osmotic effect. Mannitol is however contraindicated in decompensated shock, oliguria, anuria and heart failure.[8]

ICP monitoring: Though the role of ICP monitoring in traumatic brain injuries and infective meningoencephalitis is an accepted standard of care, the current body of evidence does not recommend its routine use in patients with HIE.[7] This evidence is mainly based on the conclusions drawn from studies in hypoxic ischemic injuries secondary to near drowning where it was found that ICP monitoring was not beneficial.[9,10] Hence more studies are needed in HIE patients before incorporating it as a standard of care.

Need for neuroimaging: An initial CT may be helpful in situations where the etiology of arrest is not clear or where there may be concomitant trauma. Serial head CT scans after cardiac arrest is indicated only if new or evolving pathology is suspected, such as hemorrhage, evolving mass lesion, or herniation. The changes of HIE in a CT scan (poor gray and white differentiation due to edema, decreased ventricular and basal cistern size and effacement of sulci) take more than 24 hours to appear. Comparatively MRI especially diffusion weighted imaging is more sensitive to detect early HIE changes, and provides detailed information about ischemic brain injury. The disadvantages of MRI are the relatively longer scanning time as compared

to CT and increased need for sedation/muscle relaxant use to prevent motion artefact.

Seizures: In HIE secondary to cardiac arrest, the incidence of non-convulsive status epilepticus (NCSE) is reported to be as high as 24% and is associated with worse outcomes.[11] This highlights the importance of continuous surface EEG neuromonitoring in these children as both convulsive and non-convulsive status epilepticus need early treatment with antiepileptic drugs (AED). For suppression of seizures benzodiazepines or other antiepileptics like phenytoin may be used. Clonazepam is effective against myoclonus.[12]

Hemodynamic management: Arterial catheter for continuous blood pressure measurement may be essential as mean arterial pressure is an important component for maintaining cerebral perfusion pressure. Likewise targeting normotension is crucial for preventing secondary injuries. Both hypotension and hypertension are detrimental and should be avoided. It will be safer to maintain MAP's > 50th centile.[8]

Mechanical ventilation: While managing children with HIE, mechanical ventilation is initiated and targeted to maintain normoxia and normocapnia. The AHA recommends titrating supplemental oxygen administration in post-cardiac arrest patients to maintain SpO_2 around 94%. Both extremes, i.e. hypoxia as well as hyperoxia are to be strictly avoided. Similarly ventilation should be targeted to maintain PCO_2 ~ 35mm Hg.[8]

Temperature management: Therapeutic hypothermia has come to the forefront as a promising strategy for improving survival and neurologic outcome after cardiac arrest in adults. In children more supporting data is required especially with reference to the optimal method for inducing and maintaining hypothermia and for post-hypothermia rewarming. Whole body cooling or selective head cooling has been recommended in neonates after birth asphyxia for improved outcomes.[13,14] Hypothermia reduces brain metabolism, excitotoxicity, oxidative stress and inflammation. Based on this evidence, AHA update 2015 recommends considering therapeutic hypothermia (32°C–34°C) for pediatric OHCA once ROSC is achieved; disadvantages being decrease in the systemic clearance of cytochrome P450 and CYP2E1 metabolized drugs, delay in the timing of clinical testing of brain death (24 hours of normothermia) and accurate prognostication.[15] As more answers are awaited on the role of hypothermia, one thing that is of unambiguous benefit is avoidance of fever. Fever (>38°C) after an acute hypoxic–ischemic insult exacerbates neuronal injury and leads to worse outcomes. Children with 'persistent' hyperthermia, defined as a temperature e"38°C for a 24-hour period post-ROSC, had worse outcomes when compared with children without persistent hyperthermia. Therefore, the current AHA recommendation emphasises on targeting normothermia.

Other organ support in these patients are of equal importance. Renal replacement therapy is indicated in oliguric acute kidney injury, hyperkalemia refractory to medical measures and fluid overload.

Role of neuromonitoring: It is very clear that while managing any child with HIE we need to maintain a delicate balance of multiple physiological variables so as to prevent secondary injuries. The question therefore is: how to deliver and monitor these targeted therapeutic interventions? Neurological examination to detect dysfunction is almost defunct and meaningless in a critical care setting where children are sedated or paralyzed. Therefore we need monitoring of cerebral oxygenation and function. Various modalities like cerebral oxygenation monitoring, EEG monitoring, regional cerebral tissue oxygenation by Near-infrared spectroscopy (NIRS) and changes in cerebral blood flow by thermodilution and transcranial Doppler have now become an integral component of neuroprotective strategies.

Prognosis and outcome of HIE

Neuroprognostication is crucial in post-HIE patients. An overly negative outcome prediction may lead us to err on the side of premature withdrawal of supportive care in an otherwise potentially salvageable child. On the contrary an overly positive outcome prediction may lead to survival of a severe neurologically damaged child with little or no quality of life. From an intensivist's perspective, an accurate outcome prediction is important for judicious resource allocation so that time and resources are allotted to a child who is more likely to benefit. There is currently no single clinical, laboratory or imaging test to predict with certainty the neurologic outcome in post HIE or post cardiac arrest patients.[14] However, a combination of variables like nature of event leading to HIE, physical exam signs, neurophysiologic studies [electroencephalogram (EEG) and evoked potentials (EP)] and neuroimaging may help in prognostication.

Nature of event: Outcomes after cardiac arrest in terms of mortality and morbidity are poor in children. Over half of the children who survive cardiac arrest develop some degree of HIE. In a large meta-analysis of all cause cardiac arrest, ROSC was achieved in 13% of pediatric patients. In this study, location of the cardiac arrest had a large impact

on survival; 24% for children with in-hospital cardiac arrest and 9% for out-of-hospital cardiac arrest.[16] Other factors associated with poor outcome were un-witnessed cardiac arrest, need for 3 or more doses of epinephrine and > 30 minutes of CPR.[16] In a study of patients having cardiac arrests within a PICU, CPR durations and severity of illness PRISM III score were significant predictors of survival.[17]

Physical Examination: A detailed neurological examination is the cornerstone of neuroprognostication. Absence of corneal reflexes, pupillary reflexes, withdrawal to pain, motor response at 24 hours and motor response at 72 hours were found to be predictors of poor outcome or death.[18]

Electroencephalogram: EEG is a non-invasive bedside method and a good indicator of thalamocortical function. The utility of single EEG is limited as it lacks specificity. Discontinuous EEG activity, epileptiform spikes or discharges and generalized burst suppression are predictors of poor outcome in EEG.

Evoked potentials: Evoked potentials (EP) are useful in an intensive care setting, as they are unaffected by sedation and environmental electrical noise. Somatosensory evoked potential (SSEP) which uses electrical stimulation of peripheral nerves to record the somatosensory pathways is the most commonly used EP and a better predictor of outcome than EEG or physical signs.[19] It can be done within 24 to 48 hours. Absence of SSEP may be more sensitive and specific in predicting unfavourable outcome post-HIE.[20]

Biomarkers: Neuron specific enolase (NSE) and S100 B are the most studied biomarkers of brain injury and also used for prognostication in post cardiac arrest patients. In a pilot study in children, serum NSE was found to be associated with poor outcome and mortality at 24, 48 and 72 hours following ROSC.[21] Combination of clinical findings with biomarkers will be a more powerful early prediction tool for long-term neurologic outcome.[22]

Neuroimaging: Both MRI and MRS have been used for outcome prediction rather than aiding decision making in intensive care management. Injury to cortical lobes and the basal ganglia have been associated with poor outcome after pediatric cardiac arrest.[23] On magnetic resonance spectroscopy (MRS) elevated lactate (marker of deficient aerobic energy metabolism) and reduced N-acetylaspartate (synthesized in neurons with reduced levels suggesting neuron injury) were associated with poor outcome.[23]

The overall predictive utility is improved by combining several variables rather than using a single criterion.

Points to Remember

- ***Hypoxic-ischemic encephalopathy is a constellation of pathophysiological and molecular injuries induced by hypoxia, ischemia and cytotoxicity and further aggravated by reperfusion.***
- ***Children with HIE present with altered consciousness and seizures.***
- ***Intensive care management focuses on maintaining a balance between systemic and cerebral targets with the help of multimodal neuromonitoring.***
- ***The neuroprotective approach emphasizes on normoxia, normocarbia, normotension, and euglycemia.***
- ***Fever must be strictly avoided in all children with HIE.***
- ***Therapeutic hypothermia can be considered as an option in OHCA after ROSC is achieved.***
- ***Biomarkers, evoked potentials and neuroimaging have been used in combination with clinical signs for outcome prediction.***

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Workshop on "Basic Biostatistics", Lucknow

Date: 26th – 28th August, 2016

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PEDIATRIC NEUROLOGY

CHILDHOOD MIGRAINE

***Sangeetha Yoganathan**

Abstract: *Headache is one of the most common causes of referral to the emergency department and neurology clinic visit in children. Migraine, tension type headache and cluster headache are the common causes of primary headache. Based on the temporal patterns, headache can be categorized into acute, acute and recurrent, chronic non-progressive and chronic and progressive. The pathophysiology of migraine is complex. The traditional medical model of history, general physical and neurological examination should be followed in evaluation of any child with headache. General physical examination begins with assessment of vitals, anthropometry and search for any external markers of vasculitis. Thorough neurological examination should be carried out to document any signs of raised intracranial pressure or focal neurological deficits. Imaging is not routinely recommended in children with well recognized episodic headache symptoms suggesting diagnosis of migraine. Nonsteroidal anti-inflammatory agents (NSAIDs), acetaminophen, 5-HT receptor agonists, dopamine receptor antagonists, and antihistamine agents are often used in aborting acute migraine attacks. Migraine headache that impairs the quality of life and functioning are indicators for the initiation of prophylaxis. This review will briefly discuss about the clinical approach, evaluation, differential diagnosis and management of children with migraine.*

Keywords: *Headache, Migraine, Migraine prophylaxis*

Headache is one of the most common causes of referral to the emergency department and neurology clinic visit in children. Migraine, tension type headache and cluster headache are the common causes of primary headache. Headache may be secondary to increased intracranial pressure, trauma, brain tumors, meningitis, vasculitis, drug or toxin exposure, substance withdrawal, head and neck infections or systemic illness. Cranial neuropathies and primary facial pain syndromes account for the third category of headache. This review will briefly discuss about the clinical approach, evaluation, differential diagnosis and management of migraine in children.

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Epidemiology

The prevalence of migraine in children and adolescents varies from 3%-23%.[1] Male preponderance has been reported in pre-pubertal age with a shift to female preponderance in post-pubertal age.[2,3] The prevalence of migraine with aura in an urban cohort of children was 1.5%.[4] In contrast, aura in adults with migraine was reported in one-third of cases.[5] Decreased prevalence of aura in children as compared to adults might be explained by the fact that the children could rarely explain the symptoms of aura. The prevalence of migraine without aura in a cohort of children was 2.2%-3.4%.[4]

Classification and etiology of headache

Based on the temporal patterns, headache can be categorized into acute, acute and recurrent, chronic non-progressive, and chronic and progressive.[6] An overlap of above types can be categorized under mixed type. Common causes of various temporal patterns of headache are listed below:

1. Acute: Fever, systemic illness, head and neck infection, meningitis, rupture of vascular malformations, dyselectrolytemia, hypertension, trauma
2. Acute and recurrent: Migraine, cluster headache, migraine variants
3. Chronic and non-progressive: Chronic migraine, tension headache, depression
4. Chronic progressive: Intracranial space occupying lesions, hydrocephalus

Based on the International classification of headache disorders (ICHD-3 beta), migraine is classified as follows:[7]

1. Migraine without aura
2. Migraine with aura
    a. Migraine with typical aura (typical aura with headache, typical aura without headache)

   b. Migraine with brainstem aura (basilar migraine)
   c. Hemiplegic migraine (familial or sporadic)
   d. Retinal migraine
3. Chronic migraine
4. Complications of migraine (status migrainosus, persistent aura without infarction, migrainous infarction, migraine-aura triggered seizures)
5. Probable migraine (with or without aura)
6. Episodic syndromes that may be associated with migraine (recurrent gastrointestinal disturbances such as cyclical vomiting syndrome and abdominal migraine, benign paroxysmal vertigo and benign paroxysmal torticollis)

Diagnostic criteria for migraine

Diagnosis of migraine is essentially clinical. There is limited role for the various diagnostic modalities in confirmation of diagnosis or clinical management of children and adolescents with migraine. Terminologies used in migraine change constantly from time to time. Diagnostic criteria for the migraine without aura, migraine with aura and chronic migraine are given in Box 1, 2 and 3 respectively.[7]

Box 1. Migraine without aura

- At least five attacks fulfilling criteria B–D.
- Headache attacks lasting 4-72 hours.
- Headache has at least two of the following characteristics: 1) unilateral location, 2) pulsating quality, 3) moderate or severe pain intensity and 4) aggravation by or causing avoidance of routine physical activity.
- At least one of the following during headache:

  1) nausea and/or vomiting and

  2) photophobia and phonophobia.
- Not better accounted for by another ICHD-3 diagnosis.

Box 2. Migraine with aura

Diagnostic criteria:

- At least two attacks fulfilling criteria B and C.
- One or more of the following fully reversible aura symptoms: 1) visual, 2) sensory, 3) speech and/or language, 4) motor, 5) brainstem and 6) retinal.
- At least two of the following four characteristics: 1) at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession, 2) duration of each aura symptom varies from 5-60 minutes, 3) at least one aura symptom is unilateral and 4) aura is accompanied, or followed by headache within 1 hour.
- Not better accounted for by another ICHD-3 diagnosis and transient ischemic attack must be excluded.

In children with migraine with brainstem aura, aura symptoms originate from brainstem but motor weakness and retinal symptoms do not occur. Migraine with aura and motor weakness will be categorized under hemiplegic migraine. Fully reversible monocular positive and/or negative visual phenomena occur in retinal migraine.

Box 3. Chronic migraine

Diagnostic criteria:

- Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months and fulfilling criteria B and C.
- Occurring in a patient who has had at least five attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura.
- On ≥8 days per month for >3 months, fulfilling any of the following:
  - criteria C and D for migraine without aura.
  - criteria B and C for migraine with aura believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.
- Not accounted for by another ICHD-3 diagnosis.

Pathophysiology of migraine

The pathophysiology of migraine is complex. Vascular theory was initially proposed to explain the symptoms of migraine. Aura was thought to be caused by transient ischemia related to vasoconstriction followed by vasodilatation of intracranial vessels leading on to mechanical activation of sensory afferents that could explain the headache phase. However, further research had shown that migraine can be induced even without dilatation of vessels thereby questioning the vascular theory.[8]

With advances in research, convincing mechanisms have been put forward to explain the symptoms of migraine.[9] The meningeal blood vessels are the primary pain sensitive structures innervated by ophthalmic division of trigeminal nerve. Activation of these afferent fibers

results in the activation of second order neurons located in the trigeminal nucleus and upper divisions of cervical cord. The impulses are then transmitted to structures involved in pain perception such as thalamic nuclei and periaqueductal grey region. Two important mechanisms in the neurobiology of migraine are the cortical spreading depression (CSD) and activation of trigeminovascular system (TGVS).

Electrical, mechanical stimuli or stimulation of potassium channels result in the generation of CSD, a slow propagating wave of neuronal depolarization that produces intense spike activity lasting for seconds followed by neural suppression lasting for minutes. CSD could explain the mechanism of aura. Activation of the TGVS results in the release of vasoactive peptides including calcitonin gene-related peptide, neurokinin A and substance P which leads on to vasodilatation of meningeal vessels, plasma extravasation and degranulation of mast cells. Another important mechanism is the sensitization of central and peripheral afferent circuits to chemical, thermal and mechanical stimuli.

Evaluation of a child with migraine

The traditional medical model of history, general physical and neurological examination should be followed in evaluation of any child with headache. Systematic assessment of a child with migraine includes the elicitation of history such as type of headache, details about onset of headache, precipitating factors, total duration of symptoms, temporal pattern of headache, frequency and duration, occurrence of headache at specific time, presence of warning symptoms, location and quality of pain, associated symptoms, aggravating or relieving factors, what the child does during headache episode, presence of neurological symptoms in between the headache, comorbid medical illness, medication history, family history and also asking the child about the reason for headache.[10]

General physical examination begins with assessment of vitals, anthropometry and search for any external markers of vasculitis. Thorough neurological examination should be carried out to document any signs of raised intracranial pressure or focal neurological deficits.

Episodic syndromes that might be associated with migraine are cyclical vomiting syndrome, abdominal migraine, benign paroxysmal vertigo and benign paroxysmal torticollis. These episodic syndromes are discussed briefly in Box 4, 5, 6 & 7.[7]

Box 4. Cyclical vomiting syndrome

Diagnostic criteria:

- At least five attacks of intense nausea and vomiting fulfilling criteria B and C.
- Stereotypical and predictable periodicity.
- All of the following: 1) nausea and vomiting occur at least four times per hour, 2) attacks last ≥1 hour and up to 10 days, 3) attacks occur ≥1 week apart.
- Symptom free interval in between the attacks.
- Not attributed to another disorder.

Box 5. Abdominal migraine

Diagnostic criteria:

- At least five attacks of abdominal pain, fulfilling criteria B–D.
- Pain has at least two of the following three characteristics: 1) midline location, periumbilical or poorly localized, 2) dull or 'just sore' quality, 3) moderate or severe intensity.
- During attacks, at least two of the following: Anorexia, nausea, vomiting, pallor.
- Attacks last 2-72 hours.
- Complete freedom from symptoms between attacks.
- Not attributed to another disorder.

Box 6. Benign paroxysmal vertigo

Diagnostic criteria:

- At least five attacks fulfilling criteria B and C.
- Vertigo without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
- At least one of the following associated symptoms or signs: 1) nystagmus, 2) ataxia, 3) vomiting, 4) pallor and 5) fearfulness.
- Normal neurological examination and audiometric and vestibular functions between attacks.
- Not attributed to another disorder.

Role of neuroimaging

Imaging is not routinely recommended in children with well recognized episodic headache symptoms suggesting diagnosis of migraine. The presence of red flags in history, general physical and neurological examination such as

Box 7. Benign paroxysmal torticollis

Diagnostic criteria:

- Recurrent attacks in a young child, fulfilling criteria B and C.
- Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days.
- At least one of the following associated symptoms or signs: 1) pallor, 2) irritability, 3) malaise, 4) vomiting and 5) ataxia.
- Normal neurological examination between attacks.
- Not attributed to another disorder.

fever, immunodeficiency state, epilepsy, malignancies, hypertension, loss of consciousness, papilledema, cerebellar ataxia, hemiparesis, brisk deep tendon reflexes, abnormal eye movements, cluster headache, trigeminal neuralgia or suspected trigeminal autonomic neuralgia warrant neuroimaging to rule out an underlying intracranial pathology.[11,12,13,14,15]

Treatment

General principles

General principles in the management of migraine in children and adolescents are to establish the diagnosis, assess the headache burden or disability, decide on the need for prophylaxis, counsel the patient and family about the diagnosis and management, discuss the treatment options and adverse effects related to treatment, encourage the patient to identify and avoid triggers, treat comorbid conditions, assess the progress periodically with the help of headache calendars, monitor for medications overuse and taper the medications if symptoms are controlled.[16]

Acute abortive treatment

Headache is one of the common causes of emergency department visits in children. After establishing the diagnosis of migraine, parents should be reassured about the benign nature of headache. Child should preferably be placed in a dark and quiet area and encouraged to sleep. Intravenous (IV) access should be established to maintain adequate hydration, to avoid acute kidney injury related to the use of non-steroidal anti-inflammatory agents (NSAIDs) and to prevent the postural hypotension related to the use of phenothiazines.[17,18] IV access is also essential for the administration of intravenous abortive medications if needed.

NSAIDs, paracetamol, 5-HT receptor antagonists, dopamine receptor antagonists, and antihistamine agents are often used in aborting acute migraine attacks.[19] Oral ibuprofen 10 mg/kg (max: 800 mg/dose or 2400 mg/day), IV ketorolac 0.5 mg/kg (max: 30 mg/dose) or oral paracetamol 15 mg/kg (max: 1 g/dose or 4 g/day) are the analgesics used in the acute management. Oral or parenteral naproxen has also been tried in the acute management of pediatric migraine.

Dopamine antagonists that are used in the acute management are IV prochlorperazine 0.15 mg/kg (max: 10 mg/dose) and IV metoclopramide 0.1 mg/kg (max: 10 mg/dose). Dopamine antagonists such as diphenhydramine are used to avoid the extrapyramidal side effects. Anti-emetics that are prescribed are IV diphenhydramine 1 mg/kg (max: 50 mg/dose) and promethazine 0.25-1 mg/kg (max:25mg/dose). Though ondansetron is not recommended for use in the acute management of migraine, it has also been found to be widely used.[20] 5-HT antagonist acts as an inhibitor of the neurovascular cascade of events and aborts the migraine attack. Triptans can be administered by multiple routes. Sumatriptan may be administered through intranasal (5-20 mg), oral (50-100 mg) or subcutaneous (3-6 mg) routes. Rizatriptan is another triptan administered via oral route (5-10 mg). Oral preparations of almotriptan, rizatriptan, and zolmitriptan are also used in management of childhood migraine.[21] Level I evidence exists for nasal administration of sumatriptan and zolmitriptan and oral administration of naratriptan, rizatriptan, sumatriptan, zolmitriptan and almotriptan in the acute management of migraine in children and adolescents.[22]

Subanesthetic dose of propofol (0.5 mg/kg as bolus and repeated every 15 minutes as required) was also found to be effective in the acute treatment of migraine in children.[23] There is no evidence to support the use of opioid analgesics in children in contrast to adults.

Migraine prophylaxis

Migraine headache that impairs the quality of life and functioning are indicators for initiation of prophylaxis.[16,24] Preventive therapies for migraine in children and adolescents are summarized in Table I.

Nutraceuticals

Complementary and alternative therapies are widely used in the management of headache.[25] Mitochondrial dysfunction is speculated as a cause for migraine. Riboflavin plays a vital role in the electron transport chain and Krebs cycle. It is postulated that riboflavin supplementation might be beneficial in reducing the

Table I: Preventive therapies for migraine in children and adolescents[16,22]

Tricyclic antidepressants	Level of evidence
• Amitriptyline: Age 3-12 y: 10 mg, Age 9-15 y: 1 mg/kg/d	IV
• Nortriptyline	
Calcium channel blockers	
• Verapramil	
• Flunarizine: Age 5-11 y: 5 mg	I
• Nimodipine: Age 7-18 y: 10-20 mg	I
Antiepileptic medications	
• Divalproex sodium: Age 7-16 y: 15-45 mg/kg/d	IV
• Topiramate: Age 8-15 y: 12.5–225 mg, Age 9-17 y: 500 to 1000 mg/d	IV / I
• Gabapentin	IV
• Levetiracetam: Age 3-17 y: 250-500 mg	IV
• Zonisamide: Age 10-17 y: 6 mg/kg/d	IV
Antihypertensives	
• Propranolol: Age 3-12 years: 80 mg, Age 7-16 years: 60-120 mg	II
• Clonidine: Age 7-14 years: 0.07–0.1 mg/day, Age ≤15 years: 0.025-0.05 mg/day	II
• Metoprolol	
Anti-histamines: Cyproheptadine (2-8 mg/day)	IV
Neurotoxins (eg, onabotulinumtoxinA)	
Selective serotonin reuptake inhibitors (SSRI)	
Fluoxetine, Fluvoxamine, Paroxetine	

frequency of migraine. The recommended dose of riboflavin is 50 to 400 mg/d for a minimum period of 4 months. A retrospective study has found that riboflavin is useful in the prevention of frequent migraine attacks.[26] In contrast, conflicting observations were identified later in randomized controlled trials.[27,28] This might possibly explained by the fact that only certain haplotypes of mitochondria that respond to riboflavin therapy.[29] High dose of riboflavin may rarely result in diarrhea, orange-coloured urine, and vomiting. Nutraceuticals and herbal preparations used in the management of migraine are coenzyme Q10, magnesium, alpha lipoic acid, feverfew, butterbur and petasites. The evidence for use of nutraceuticals in children and adolescents is low.[30]

Elimination diet in migraine

Cheeses, pizza, processed meats, chocolates, caffeine, monosodium glutamate, alcohol, red wines, beer, nuts, figs, aspartame, sauerkraut and yeast extracts are to be avoided in patients with migraine, although the role of elimination diet is controversial.[31]

Non-pharmacological interventions

Growing body of evidence supports the use of complementary and alternative therapies in patients with migraine. Behavioral treatments include cognitive behavioral therapy and biobehavioral training. Biobehavioral procedures are widely accepted and

beneficial in childhood headache.[32] Electromyographic biofeedback, electroencephalography, thermal hand warming and galvanic skin resistance feedback are the biofeedback techniques employed in the management. Various relaxation therapies such as progressive muscle relaxation, autogenic training, meditation, self-hypnosis and passive relaxation are also beneficial. Acupuncture, oxygen therapy, transcutaneous electrical nerve stimulation, occlusal adjustment, cervical manipulation, physical therapy, massage, chiropractic therapy, and osteopathic manipulation have been tried in the management of patients with headache.[33]

Surgical management

Elimination of migraine headache following forehead rejuvenation surgeries has led to the proposal of surgery as a potential preventive option for selected patients.[34] Elimination of migraine following botulinum toxin injection for cosmetic reasons could possibly be explained by the fact that chemical denervation has resulted in the ablation of muscle contraction.[35] However, the fact that not all patients with these procedures had resolution of migraine headaches has emphasized the need for identification of specific trigger sites. Removal of muscles of frontal region, foraminotomy, removal of the supraorbital and supratrochlear arteries, fasciotomy, excision of segment of the zygomaticotemporal branch of the trigeminal nerve, correction of deviated nasal septum, removing the nasal spurs, decompressing the turbinates, eliminating the concha bullosa and removal of semispinalis capitis to decompress the greater occipital nerve are some of the surgical options used in management of patients with migraine headache.[36]

Prognosis

A ten year follow-up study in adolescents with migraine had documented remission of symptoms in 38%, persistence of headache in 42% and transformation to tension type headache in 20%. This study concluded that migraine in adolescents had a favorable outcome and familial predisposition resulted in unfavorable outcome.[37] More epidemiological studies are needed to analyze the long-term outcome of migraine in children.

Points to Remember

- ***Migraine is a common cause of headache in children and adolescents.***
- ***Migraine without aura is the most frequent form.***
- ***Diagnosis is essentially clinical and other causes of headache such as neoplastic, vascular, metabolic or toxic disorders must be excluded.***
- ***Need for prophylaxis is decided by the headache burden and disability.***
- ***Balanced treatment with pharmacological measures and biobehavioural interventions should be endorsed.***

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GENERAL ARTICLE

UNEXPECTED DIFFICULT PEDIATRIC AIRWAY: PEARLS AND PITFALLS FOR THE EMERGENCY DEPARTMENT PHYSICIAN

***Debasis Das Adhikari**
****Ekta Rai**

Abstract: *Unexpected difficult pediatric airway without predictors is rare but when encountered is a nightmare. These crises can be salvaged safely most of the time if the background knowledge, concepts and strategies are not only read but also rehearsed, practiced and discussed frequently. As the pediatric emergency doctors rarely face the problems of maintaining unanticipated difficult airway, they have to be well versed with the guidelines. This review article proposes to present the simple stepwise approach to such a situation based on the current evidences and literature.*

Keywords: *Difficult airway, Unanticipated, Children, Emergency.*

Inadequate management of child's airway can not only lead to increased morbidity and mortality but is also one of the main sources of stress for a pediatric physician who does not routinely manage pediatric airway.[1] Because of the availability of experts and newer equipments in airway management for intubation, the emergency trainees are exposed to airway management far less than they used to be before, but fortunately most of the pedaitric airway is easy to manage. Nevertheless, it is of vital importance to teach the pediatricians and emergency physicians to assess the airway and anticipate difficulty in airway and manage the basic airway skills that are probably one of the most important skills while managing a sick child.[2] A good pre-intubation assessment should be able to predict difficult airways at most of the scenarios but rarely unanticipated difficult airway can be encountered and may lead to serious complications.[3]

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The pediatric airway differs from that of adults in the following aspects:

a) relatively large head and tongue, b) more rostral larynx, c) bulky and hanging epiglottis, d) angled vocal cords, e) funnel shaped larynx: Narrowest part of pediatric airway is cricoid cartilage. However lately there has been a question raised on whether the narrowest part of pediatric airway is the cricoid.[4]

Definitions of difficult airway

American society of anesthesiologists (ASA) task force defines a difficult airway as "The clinical situation in which a conventionally trained anesthesiologist experiences difficulty with mask ventilation, difficulty with tracheal intubation, or both".[5] The task force further noted that the "difficult airway represented a complex interaction between patient factors, the clinical setting, and the skills and preferences of the practitioners".

Difficult airways also can be defined as when inadequate ventilation which cannot be reversed by mask ventilation and oxygen saturation cannot be maintained above 90% and also "when a trained anesthetist uses a conventional laryngoscope on more than 3 maneuvers to intubate or when more than 10 minutes is required to complete tracheal intubation".[6] Difficult mask ventilation, laryngoscopy and intubation are three parts of difficult airway.

Predictors of difficult airway

Airway characteristics that may identify a difficult airway can be rapidly assessed using the mnemonic LEMON:[7]

- **L**: Look externally for indicators of a difficult airway
- **E**: Evaluate mouth opening, thyromental distance and the distance between the mandible and the thyroid cartilage
- **M**: Mallampati score (Grade: I, II, III, IV)
- **O**: Obstruction: Signs of airway obstruction
- **N**: Neck mobility

The other predictors of difficult airway are mainly

short muscular neck, prominent upper incisors, protruding mandible, receding mandible, small mouth opening, large tongue, limited neck mobility, limited mouth opening due to restricted tympano-mandibular joint movement and syndromic appearance.[8]

Difficulties in predicting airway problem

Predicting the level of airway difficulty in children is not always easy because the predictors used in adult patients may not be applicable to children.[8] Some of the predictors that have shown good sensitivity and specificity such as mandibular protrusion, Mallampati's classification (Fig.1.) and movement of the atlanto-occipital joint are very difficult to assess in children, particularly for children less than 3 years of age. Though a good history and examination will reveal most of the difficult airway, an unanticipated difficult airway still exists and backup plan to oxygenate and ventilate should be ready.

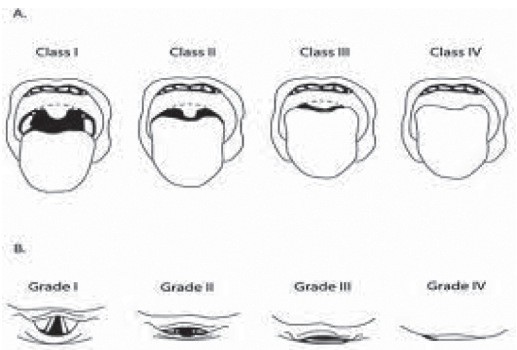


Fig.1. Mallampati classification of airway

Difficult airway classification

They are mainly classified as a) Anticipated and b) Unanticipated

Anticipated: These include anatomic disruptions that compromise the airway structures like maxilla, mandible, palate, tongue, neck, oral opening, etc. The reasons for anticipated failure to intubate may be congenital or acquired airway problem, acute or chronic infection, supra or subglottic obstruction. Common examples include syndromes (Pierre Robin, Treacher Collins, Goldenhar), burns, scarring or trauma to face, hemangiomas, epiglottitis or croup.[9]

Unanticipated (rare with experience): In unanticipated difficult airway there are no predictors of difficult airway, no symptoms or signs of respiratory distress and no history of recent respiratory problems. Unanticipated failed intubation in a child is extremely rare in experienced hands. Unanticipated difficult airway is a nightmare to meet as there is no preparation and planning for the disaster management. The main cause for morbidity and mortality is due to failed oxygenation. Management of failed intubation must include: oxygenation plan, intubation plan and rescue plan. Inadequate history along with examinations and inability to understand the clinical implications are the most common causes of unanticipated failed intubation.

Management of unanticipated difficult airway: Unanticipated difficult airway could be due to difficult mask ventilation, intubation or both. The algorithm for the management of unanticipated difficult airway in pediatric emergency is summarized in Fig.2 and Fig.3.

Management of difficulty in mask ventilation[10]

Following maneuver can be used to improve oxygenation while facing an unexpected difficulty in bagging:

- Remove foreign body by Magill forceps
- Deepen the depth of anesthesia
- Triple maneuver if c-spine clear (head tilt, jaw lift, mouth opening)
- Nasal or oropharyngeal airways
- Two-person four-hand technique
- Do not abandon bagging unless it is impossible with two-person four-hand technique along with an oropharyngeal / nasopharyngeal airway[11, 12]

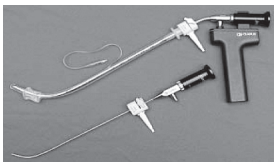
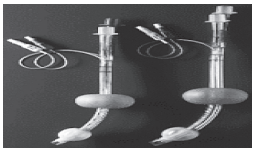
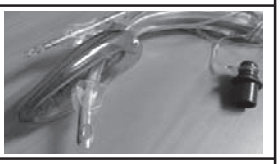
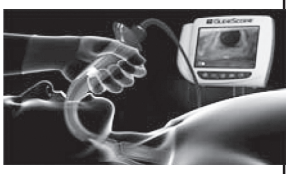
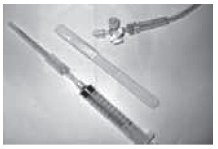
Unanticipated difficult airway due to difficulty in intubation

Before attempting intubation, best environment has to be attained in terms of good depth of anesthesia, i.v. access and full monitoring if possible. An optimal or best attempt at difficult laryngoscopy should consist of: using optimal sniffing position, use of optimum external laryngeal manipulation (backwards, upwards, rightwards pressure - BURP), adequate length of blade, appropriate blade and a reasonably experienced laryngoscopist.

Plan A for an unsuccessful intubation[13]

Experienced personnel should be called for help and optimal head position with BURP maneuver on thyroid cartilage is maintained if the first laryngoscopy failed.[14] Maximum of three attempts with some modifications in the laryngoscopy techniques is acceptable.[15]

Table I. Gallery of tools for difficult airway

Names	Advantages	Disadvantage	Pictures
Macintosh	Blade of choice Minimizses stimulation of posterior epiglottis Configured as per tongue curvature		
Magill	When glottis is deep Upper incisor are prominent Long floppy epiglottis		
Miller	Well protected view	Requires wider path to accept tube passage lateral to blade	
Mc Coy	Flexion of the tip of blade possible so anterior laryngeal inlet can be seen easily	Intubation may still need stylet or external laryngeal pressure	
Optical stylet	Unpredicted difficult airway Reduced trauma Reduction in intubation force Easy to learn	Economic issues	
Gum elastic bougie	Useful modality to intubate even in grade III laryngoscopy	Not useful if epiglottis is not seen at all	
LMA	Life saving device Needs less expertise	Does not protect the airway in full stomach patients	
Combitube	Useful in crises situation	Not used regularly so handling the tube may be issue	
iLMA	Useful adjuvant in intubation Maintains oxygenation easily even in minimally experienced hands	Not available in pediatric sizes	
Video laryngoscopy	Offers better laryngoscopic view	Not useful if inadequate mouth opening Complications observed if the steps are not followed appropriately	
Cricothyroid-otomy	Emergency situation Severe fascial and nasal injuries Spine trauma	Invasive- Incision Trauma	

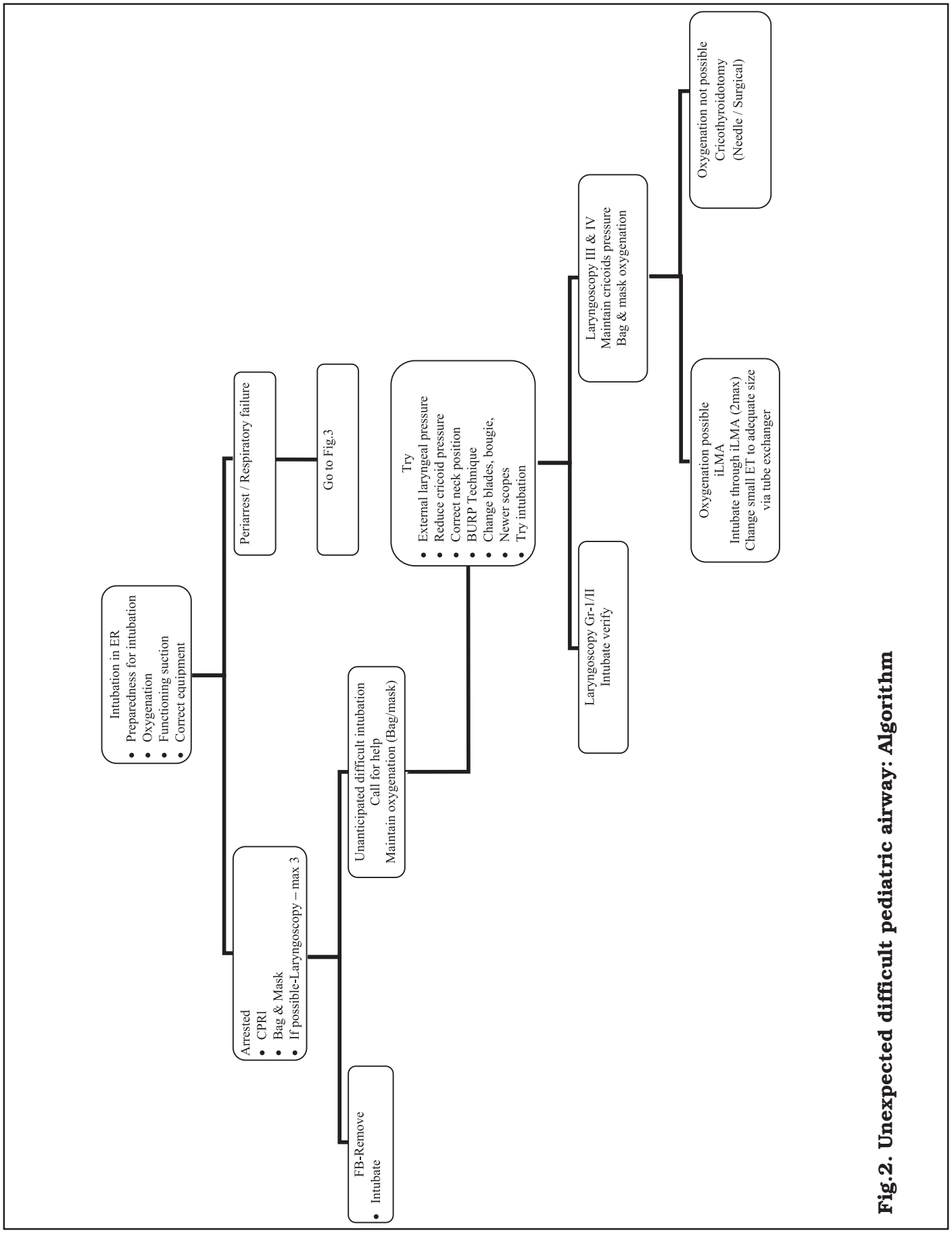
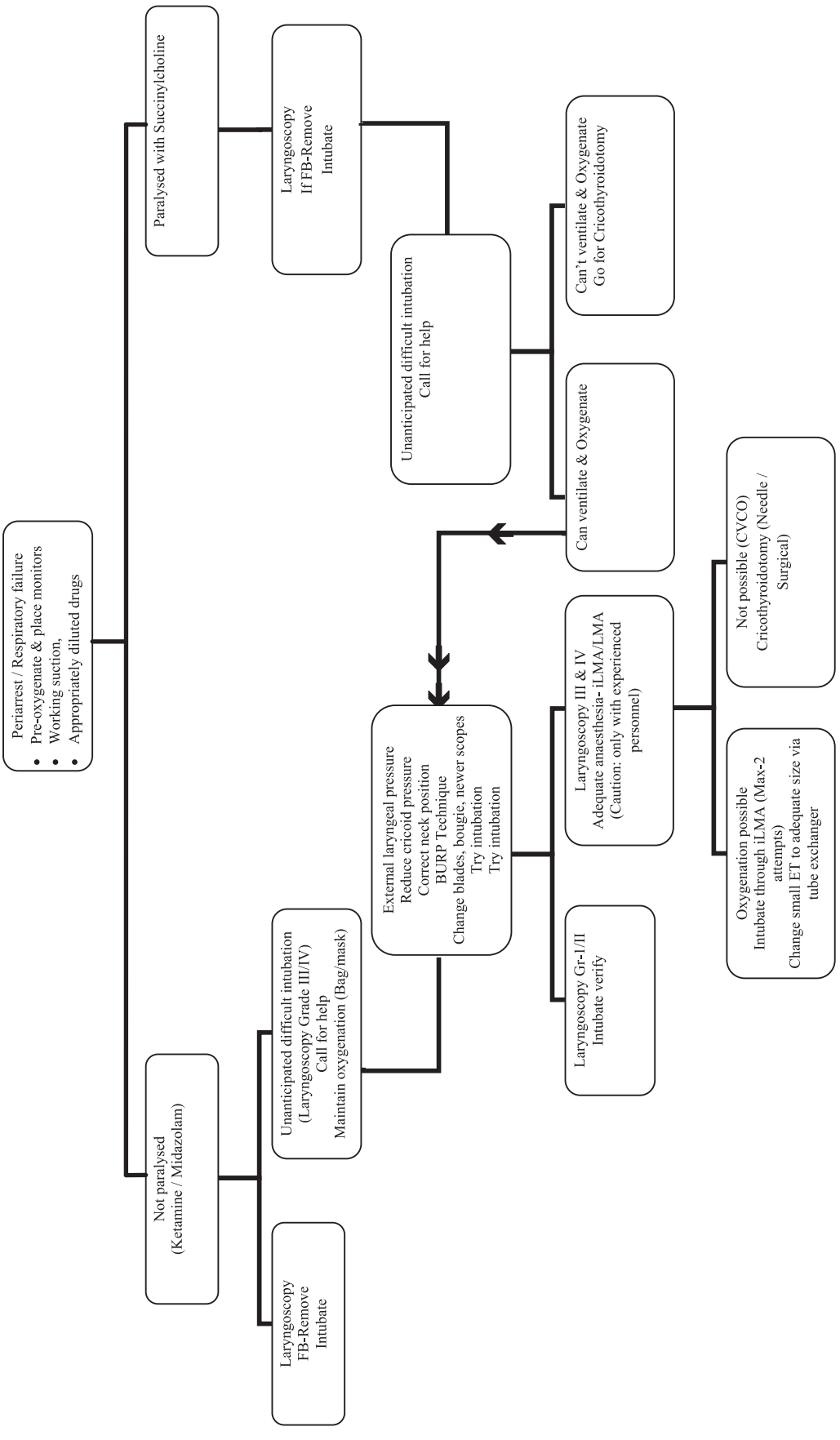


Fig.2. Unexpected difficult pediatric airway: Algorithm



CVCO: Cannot ventilate – cannot oxygenate

Fig.3. Unexpected difficult pediatric airway: Algorithm

Optimal position is different at different age group. For <2 years old children head extension without elevation of head roll is advisable whereas for >2 years sniffing head position gives the best laryngoscopic view.

Use of different laryngoscopic blades e.g. Miller, McCoy, Bullard, Glidescope and Fiber optic scope, use of bougie, and small size ETT can improve the chances of intubation (Table I).

Plan B for an unsuccessful intubation[13]

If 'plan A' fails then, one can try 'plan B' by doing following maneuvers / technique:

a) LMA[16] can be used for oxygenation and also as conduit for the fibreoptic guided intubation. Intubation can be done directly over laryngeal mark airway (LMA). The size of endotracheal tube (ETT) depends on the size of the LMA.

b) Bougie or oxygen exchange catheter can also be passed through LMA for ETT exchange (If unsuccessful after 2 attempts - STOP)

c) Light guided technique (lighted stylet)

d) Combi tube

e) Fiberoptic techniques

f) Retrograde intubation

Inability to ventilate through the endotracheal tube - Causes (DOPES)

D-Displacement of tracheal tube; O-Obstruction of tracheal tube (secretions, blood, tracheal wall, pouch and tracheal foreign body); P-Pneumothorax; E-Equipment problems and S-Stomach (increased intra-abdominal pressure)[8]

The cause should be identified and treated.

Plan C: Cannot ventilate and cannot intubate (CVCI)/Rescue

Ability to ventilate can change to inability to ventilate after multiple attempts of ventilation. At various stages of managing difficult airway, it is wise to check the ability to ventilate. The management differs significantly if the ability to ventilation is lost.

CVCI (cannot intubate cannot ventilate) is an immediate life threat to patient. This is a crisis situation, which if not handled immediately and appropriately, can lead to death.

In children oxygen saturation levels fall very rapidly as the functional residual capacity is low and basal metabolic rate is high; thus demand is more but supply is limited. Need for attempts at subglottic airway rescue techniques is required if waking up the child is not an option. Till the equipment arrives, attempt at ventilation with FiO_2 100% should continue.

Since in pediatric emergency room, ENT specialist is not available most of the time, emergency tracheostomy is not feasible. Percutaneous cannula cricothyroidotomy is the first line of management to oxygenate in age group of 1-8 years.[16] The percutaneous cannula are of two types fine bore (<4 mm) and large bore (>4 mm). Fine bore cannula needs high pressure oxygen delivery source.[17,18]

Trans-tracheal jet ventilation and passive oxygen insufflation are temporary measures which should follow the action plan, i.e. tracheotomy by specialists.

Summary and recommendation

Unexpected problems with pediatric airway management can occur with positioning, positive pressure ventilation, laryngoscopy, visualizing and/or intubating the trachea, or identifying landmarks for performing a surgical airway.

1. For children who require intubation, airway management must include a rescue plan and preparation for a failed airway.
2. LMA is to be used as the initial rescue device for a child with a failed airway who does not have complete upper airway obstruction.
3. Other alternative airway techniques that may be useful for managing a difficult airway include fiber optic laryngoscopy, video laryngoscopy, a lighted stylet, a combi tube, or performing a surgical airway.
4. A surgical airway is the only option for a child who has a failed airway with complete upper airway obstruction.

Points to Remember

- ***Be familiar and be prepared with alternative methods of intubating techniques and use it regularly in your day-to-day practice as part of failure plans, e.g. laryngeal mask airway, gum elastic bougie, fiber optic intubation so that you will not fumble at the time of crisis and will not panic.***
- ***Oxygenate at all times as oxygenation is more important than intubation in the time of crisis.***

- ***"It is preferable to use superior judgment – to avoid having to use superior skill."***
- ***Step-by-step process is in order.***
- ***Help should be called for early.***

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BOOK REVIEW

Name : Atlas & Synopsis of Neonatology

Editors-in-Chief : Rhishikesh Thakre and Srinivas Murki

Publisher : Jaypee Brothers Medical Publishers (P) Ltd

Review: A smart pocket sized guide for junior doctors and trainees in neonatology published by the neonatology chapter of IAP, with a foreword by Dr.Amdekar and presented in a very easily readable format. Well indexed and divided into seven sections covering around 250 neonatal topics and complemented by around 500 good quality photographs, it sensitizes the reader to various bedside cues and clues that bring alive, a plethora of clinical signs and conditions. As suggested by Dr.Amdekar, trying to observe the clues in the photographs before reading the text, helps sharpen observational skills of the reader. Kudos to Dr.Murki and Dr.Thakre for this yet another commendable effort.

DRUG PROFILE

ANTACIDS AND H2 RECEPTOR ANTAGONISTS

***Dr.Jeeson C Unni**
****Dr Ranjit Baby Joseph**

Abstract: *Strong evidence for the use of antacids and to a lesser extent, Histamine H2 receptor antagonists in the treatment of conditions requiring a reduction in gastric acid production is lacking. Other indications for specific antacid molecules are also discussed.*

Keywords: *Antacids, Histamine H2 receptor blockers, Proton pump inhibitors.*

Symptomatic acid reflux in children often requires medical management. There are mainly three classes of drugs used which include proton pump inhibitors (PPIs), H2 receptor antagonists (H2RAS) and antacids. Other agents include drugs that enhance the mucosal defense such as prostaglandin analogues like misoprostol and cytoprotective agents like sucralfate. Of these agents, PPIs are the most potent suppressors of gastric acid secretion by inhibiting H^+ K^+- ATPase (proton pump). PPIs available for clinical use include omeprazole, its isomer esomeprazole, lanzoprazole, rabeprazole and pantoprazole. Less potent drugs are H2RAs like cimetidine, ranitidine, famotidine and nizatidine which inhibit acid production by reversibly competing with histamine for binding to the H2 receptors on the basolateral membrane of the parietal cells. Commonly used antacids are aluminium, calcium and magnesium salts which are believed to act by neutralizing the already existing acid in the stomach.[1]

Antacids

Antacids do not reduce acid production, but may be used as an adjuvant along with histamine-2 receptor antagonists (H2RAs) or PPIs. They may be administered as a therapeutic trial and for symptomatic treatment but they do not rectify the cause of the disease. Some antacids have additional benefits and uses related to its composition. Calcium containing (e.g. calcium carbonate and calcium acetate) and aluminium containing (e.g. aluminium hydroxide) antacids were used as GI phosphate binders for the prevention and treatment of metabolic bone disease in children with chronic kidney disease till newer non-calcium-containing phosphate binders became available.[2,3] Calcium salts are widely used but produced hypercalcemia. Aluminum salts are effective binders but induced aluminum toxicity.

Aluminium hydroxide[4]

Dosages: Antacid - 4% w/w : 6-12year - 5ml 3 times daily; 12- 18year - 5-10ml 4 times daily and as required between meals and at bedtime.

Hyperphosphatemia - Oral - 1month - 1year - 2.5-5ml 3-4 times daily; 1-5year - 5-10ml 3-4 times daily; 5-12year 10-20ml 3-4 times daily - dose may be increased or decreased as required within the ranges given. 12-18year Tablet cont 840mg, 1-3 tablets 4-5 times daily.

Contraindications: In children with severe renal impairment and in the newborn due to the risk of aluminium accumulation resulting in high serum aluminium levels, porphyria and conditions associated with hypophosphatemia.

Side effects: There have been cases linking the prolonged use of antacids containing aluminium with rickets. Constipation and loss of appetite are not uncommon. Confusion, unusual tiredness or discomfort and muscle weakness may also occur.

Drug interactions: Aluminium hydroxide interferes with absorption of other medicines, making them less effective. Other medications need to be administered 1 hour before or 2 hours after aluminum hydroxide. It would interfere with effect of allopurinol, alprazolam, chlordiazepoxide, chloroquine, cimetidine, clonazepam, dexamethasone, diazepam, digoxin, ethambutol, famotidine, hydrocortisone, isoniazid, levothyroxine, lorazepam, methylprednisolone, oxazepam, penicillamine, prednisone, products containing iron, tetracycline and vitamins.

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Calcium carbonate and acetate[5]

Antacids containing calcium are not recommended for long-term use in children because they can interfere with the rate that calcium is absorbed and result in hypercalcemia and hypophosphatemia. Hence they are currently not recommended as per IAP drug formulary and British National Formulary. Current indications include hypocalcemia and conditions associated with hyperphosphatemia.[6]

Dosages: Hypocalcemia (dose depends on clinical condition and serum calcium level): Dose expressed in mg of elemental calcium: Children: 45 to 65 mg/kg/day in 4 divided doses. Neonatal hypocalcemia (dose depends on clinical condition and serum calcium level): Dose expressed in mg of elemental calcium: 50 to 150 mg/kg/day in 4 to 6 divided doses; not to exceed 1 g/day.

Hyperphosphatemia in end-stage renal failure: Dose expressed in mg of calcium carbonate: 1 g with each meal; increase as needed; range: 4 to 7 g/day. Periodic checking of serum calcium level is recommended, especially if signs or symptoms of hypercalcemia are detected. The use of calcium carbonate is not indicated for the treatment of hyperphosphatemia in patients with calculated or estimated creatinine clearance equal to or greater than 25 ml/m^2/min.

Contraindications: Severe hypercalcemia, hypercalciuria and osteoporosis due to immobilization. In patients on high doses of vitamin D or prolonged calcium treatment, serum calcium levels should be checked and interpreted in conjunction with plasma protein levels. Serum phosphate levels should be checked in all patients receiving phosphate binders, to prevent the development of a phosphate depletion syndrome.

H2 receptor antagonists(H2RAs)

H2RAs reduce gastric acid production but evidence for their efficacy and safety in infants and children is limited and of poor quality.[7] They are frequently used in the treatment of gastroesophageal reflux disease (GERD) in children. H2RAs do not reduce the frequency of reflux but do reduce the amount of acid in the refluxate by inhibiting acid production.

A Cochrane review suggests that there was moderate evidence for use of protein pump inhibitors (PPIs) and 'some evidence' for use of H2RAs for treatment for GERD in older children.[8] Lack of good head to head trials makes exact comparison difficult. Based on endoscopic studies in adults it was found that double doses of H2RAs and standard doses of PPIs are effective in preventing duodenal ulcers in patients on long term NSAID but are less effective than misoprostol.[9] No RCTs in children on prevention of gastric ulcers are available. For upper GI bleeding after endoscopic therapy, PPIs are a better option.[10]

Ranitidine[11]

Dosages: Newborn: Oral/IV 1mg/kg 3 times daily (studies with oral treatment in newborn are limited) and IV infusion 30-60 µg/kg/hr (max 3mg/kg/day).

Child 6 month - 12 year: Oral 2-4 mg/kg/dose (max 150mg)

12-18year: 150mg/dose 2 times daily. Upto 9mg/kg may be used. IV bolus 1mg/kg 2-4 times daily; IV infusion 125-250 µg/kg/hr. Reduce dose to 50% in severe renal failure (GFR<50ml/min/1.73m2).

Administration: Oral: Effervescent tablets are dissolved in a minimum of 75mL of water. Absorption of oral dose forms is not significantly affected by food or antacids. In cystic fibrosis give 1-2 hours before food. IV: dilute to 2.5mg in 1mL with NaCl 0.9% or glucose 5% and give as IV bolus over at least 3 minutes, or further dilute and give as an infusion.

Contraindications: Hypersensitivity to ranitidine or any excipient and acute porphyria. Treatment with ranitidine may mask the symptoms of other gastric diseases. Elevation of liver enzymes may occur with high doses. Effervescent tablets should be avoided in patients with a restricted sodium intake and in patients with phenylketonuria.

Side effects: Hypersensitivity reactions including urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and anaphylactic shock are reported, sometimes after a single dose. Transient and reversible changes in the liver function tests, rarely acute pancreatitis, leucopenia, thrombocytopenia, bradycardia and AV block may be seen. Mental confusion, depression and hallucination and skin rash including erythema multiforme have been reported.

Cimetidine[12]

Dosages: <1month oral /IV 5mg/kg/dose and < 12yr 5-10mg/ kg/dose 4 times daily; 12-18 year 400mg/dose 2-4 times/day. IV: give over at least 10 minutes but continuous infusion may be preferred. Dilute in NaCl 0.9% to produce a solution not exceeding 10mg in 1 ml. Oral: in cystic fibrosis administer 1-2 hours before food.

Cautions: Rapid IV administration of cimetidine may lead to hypotension and arrhythmias. Dose needs to be reduced in hepatic impairment. In mild to moderate renal impairment use 75% of the stated doses and in severe impairment use 50% of the dose, at the same time intervals.

Table I. Indications and dose of famotidine

Conditions	Dose	Max dose/day
Peptic ulcer	0.5 mg/kg/day at bedtime or 2 divided doses	40 mg
GERD	1mg/kg/day in 2 divided doses	80 mg
Duodenal/ gastric ulcer 16-18years- oral dose	20mg/day at bedtime or 10mg twice daily for 4-8weeks- max	40mg
Hypersecretory conditions	20mg 6th hourly and may gradually increase upto 160mg 6th hourly	
Esophagitis	20-40mg twice daily - upto 12 weeks.	

Side effects: GI side-effects with cimetidine includes diarrhea. Children may also report headache and tiredness.

Drug interactions: Cimetidine binds to cytochrome p450 very strongly, inhibiting the breakdown of those drugs metabolized by this enzyme in the liver, including warfarin, opioid analgesics, cyclosporin, theophylline, phenytoin, caffeine, intravenous lignocaine and hence the need to monitor toxicity of these drugs closely.

Significant pharmacokinetic interactions between ranitidine and several other drugs have been established even though several drugs which are known to interact with cimetidine have been found not to interact significantly with ranitidine, including propranolol, lignocaine, phenytoin and diazepam.[13]

Famotidine[14]

Dosages: Infants and children <16year- oral/iv as given in Table I. Dose adjustment is needed in renal impairment- when creatinine clearance 10-50ml/m^2/min: administer normal dose once daily or 50% of dose at normal dose interval. Creatinine clearance <10ml/m^2/min- administer normal dose once in 36-48 hours.

Administration: May be given orally with food and antacids. Avoid excessive amounts of coffee and aspirin while taking the drug. When giving IV, dilute to a maximum of 4mg/ml and administer either as IV bolus at 10mg/min over 2min or as infusion over 15-30 minutes.

Contraindications: Hypersensitivity to famotidine or any of the components or other H2 antagonists are definite contraindications.

Side effects: CVS: Bradycardia, tachycardia, palpitations, hypertension. CNS: Headache, vertigo, anxiety, dizziness, seizures, depression, insomnia, drowsiness, confusion, fever. Skin: Acne, pruritus, urticaria, dryness of skin, alopecia. GI: Constipation, nausea, vomiting, diarrhea, abdominal discomfort, flatulence, belching, dysgeusia, dry mouth, anorexia. Genitourinary: Impotence. Blood: Thrombocytopenia, pancytopenia. Hepatic: Elevated liver enzymes, hepatomegaly, cholestatic jaundice. Neuromuscular: Weakness, arthralgia, paresthesia, cramps. Eye: Orbital edema. Ear: Ototoxicity, tinnitus. Renal: Rise in BUN and creatinine. Respiratory: Bronchospasm.

Drug interactions: Decreases absorption of ketoconazole, triamterene, defaviridine, itraconazole, cefpodoxime, cyanocobalamine, indomethacin, melphalan and decreases effect of tolazoline.

Conclusion

Acid reflux in children may be associated with troublesome symptoms and complications. Initial management in uncomplicated cases should be medical in patients across all pediatric age groups. With the available clinical data and the demonstrated efficacy and safety, PPIs continue to be the agents of choice in controlling acid reflux. Other agents like H2RAs and antacids may be tried but are not of proven benefit. More studies are required in children to establish definite treatment guidelines.

Points to Remember

- ***PPIs are the drug of choice in primary acid reflux disease.***
- ***Efficacy of H2RAs is not proved in the treatment of GERD but may be used in conditions associated with acute gastrointestinal bleed.***
- ***H2RAs may reduce severity of the refluxate.***
- ***Antacids are not routinely recommended for treatment of GERD. Calcium salts are recommended as phosphate binders and its use as antacids should be avoided.***

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NEWS AND NOTES

16th Annual National Conference of Adolescent

Health Academy, IAP, Agra, Uttar Pradesh

Date: 17th & 18th September, 2016

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DERMATOLOGY

NUTRITIONAL DERMATOSIS IN CHILDREN

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Abstract: *Skin is the most important organ providing sensory perception, enclosing barrier and environmental protection, regulating temperature and producing vitamin D. Nutrition is a dynamic process concerned with ingestion, digestion, absorption and assimilation of food for nourishing the body. Skin reflects the internal well being and balanced nutrition in the form of smooth shiny skin, glossy hair, well developed muscles, bones and teeth, strong build and energetic to look at.*

Keywords: *Micronutrients, Deficiency status, Macronutrients, Nutritional dermatoses.*

Nutrients can be macronutrients and micronutrients. Macronutrients are needed in large quantities. They provide the substrate for building and maintaining structure and including carbohydrates, proteins and lipids. Micronutrients are necessary for good health and are required in minute quantities including vitamins and minerals. Recognition of cutaneous findings associated with nutritional abnormalities is vital because these deficiencies may be easily corrected. The basic problems in nutritional deficiency are given in Table I.

Macronutrient deficiency disorders

1. Protein energy malnutrition(PEM) - a spectrum of disorders describing varying degrees of protein and calorie deficiency.

(a) Marasmus: The term marasmus in Greek means-"wasting". The cutaneous findings of marasmus include:

1. Dry, thin, loose, wrinkled skin resulting from loss of subcutaneous fat and muscle mass with an emaciated appearance.[1]

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Table I. Nutritional disorders and the predisposing conditions

Nutritional problems	Predisposing conditions
Derangements in normal diet	Inadequate dietary intake Eating disorders Unusual dietary habits Parenteral nutrition
Hypercatabolic states	Malignancy AIDS Renal/ Hepatic disease
Malabsorption	Cystic fibrosis Inflammatory bowel disease Celiac disease Post gastro-intestinal surgery
Chronic medications	Anticonvulsants Antibiotics
Others	Genetic metabolic defects Enzyme deficiencies Anorexia and bulimia nervosa

2. Hair: Thin, fine, brittle hair and alopecia; increased lanugo hair.
3. Nails: Fissuring with impaired growth.[2]
4. Loss of buccal fat pads gives aged appearance - "Old man facies".
5. Angular cheilitis.

Kwashiorkor: Kwashiorkor derives its name from Ghanese term for "the one who is deposed," referring to child who is weaned off from breast milk onto a carbohydrate-rich but often protein-poor diet when the next sibling is born.

Cutaneous findings: Cutaneous findings - known as "Dermatosis of kwashiorkor" (DoK).

1. Mild hypoproteinemic edema
2. Pigment alterations- hypo and hyperpigmentation
3. Character of thickened epidermis- Crazy pavement pattern

Table II. Fat soluble vitamin deficiency

Vitamins	Function	Cutaneous findings	RDA	Treatment
A	Growth and differentiation of keratinocytes, maintenance of reproductive and immune system, vision and bone formation	Mild- xerosis & scaling Severe - dermatomalacia (Skin fissuring) Xerostomia, hyposmia, hypogeusia Phrynoderma (Toad skin)	1000-5000 IU	100,000–300,000 IU of oral vitamin A daily until symptoms resolve and serum levels normalize
D	Calcium homeostasis and metabolism by intestine, bones, renal tubules	Congenital atrichia Rudimentary cysts of hair over face and scalp X-linked icthyosis[3] Lamellar icthyosis Epidermolytic hyperkeratosis	5 to 10 µg/day	200 to 400 µg vitamin D per day until resolution of symptoms, about 2 to 3 months
E	Antioxidant, gene expression,enzymatic activities, neurological function	Hemolysis, purpura	Children: 5-11mg /day Adults: 15 mg/day	
K	Co-factor in carboxylation of glutamate residues on coagulation factors II, VII, IX, X, and proteins C and S, bone metabolism	Purpura, ecchymoses, gingival bleeding, gastrointestinal, genitourinary and intracranial hemorrhage, hemorrhagic disease of newborn	Children: 30-75 µg/day Adults: 90-120 µg/day	Newborns: 0.5-1 mg sc or IM Children: 2 mg Adults: 5-10 mg/day Intravenously in emergencies Fresh frozen plasma

4. Superficial desquamation of skin giving appearance of enamel paint which progresses in severe cases to form erosions mainly in extremities and buttocks giving- Flaky paint appearance
5. Hair: Sparse, dry, lustreless. Red tint to grey white. Alternating colours due to intermittent periods of poor nutrition -" Flag sign"

Essential fatty acid deficiency

Essential fatty acids (EFAs) are important substrates for many physiologic processes but cannot be synthesized by humans. Linoleic and linolenic acid are the major dietary EFAs. The main function of EFAs is maintaining cell membrane fluidity. They are also involved in the synthesis of prostaglandins and leukotrienes. They contribute to permeability of stratum corneum thereby acting as mediator of skin barrier function. Population at risk for EFA deficiency are people with poor dietary intake, malabsorptive states, preterm and low birth weight babies. The cutaneous findings of EFA deficiency is in box 1. The treatment of EFA deficiency is by oral or intravenous supplementation of EFA and topical application of sunflower / safflower oils rich in EFA.

Box. 1. Cutaneous findings of EFA deficiency

1. Xerosis, icthyosis, phrynoderma, intertriginous erosions
2. Poor wound healing, traumatic purpura secondary to capillary fragility
3. Brittle nails
4. Hyper or hypopigmentation of hair, alopecia

Micronutrient deficiency disorders

Micronutrients consist of vitamins and minerals.

Vitamins: Vitamins are organic compounds required in the diet in small amounts to perform specific biologic functions for normal maintenance of optimum growth and health. Vitamins are divided in two groups: (a) Fat soluble and (b) Water soluble. Fat soluble vitamins are vit. A, D, E, K. All others are water soluble vitamins.

The functions, the recommended dietary allowance (RDA), cutaneous features of deficiency and management of deficiency of vitamins and minerals are given in Table II, III and IV.

Table III. Water soluble vitamin deficiency

B1 (Thiamine)	Coenzyme for NADPH synthesis, carbohydrate metabolism, deoxyribose and ribose synthesis complete recovery	Red, burning tongue, peripheral edema in wet beri-beri	0.5-1 mg per 1000 kcal energy	IV or IM Thiamine 50-100mg/day for 7-14 days followed by 100 mg/day orally until
B2 (Riboflavin)	Coenzyme in Oxidation-reduction reactions, cellular respiration, oxidative phosphorylation	**Acute**[4] Erythema, epidermal necrolysis,mucositis **Chronic**[4] Angular stomatitis, cheilosis with erythema, xerosis, and fissuring, glossitis, seborrheic dermatitis-like dermatitis affecting typical sites and flexural areas of limbs and genitalia, photophobia and conjunctivitis, corneal vascularization	0.4-1 mg per 1000 kcal energy	Infants and children: 1-3 mg/day Adults:10-20mg/day
B3 (Niacin)	Synthesizes NAD, NADP- hydrogen donors and acceptors in oxidation-reduction reactions, cell differentiation and DNA processing	Photosensitive dermatitis, painful fissures of palms and soles, vesicular, crusted lesions turning to scaly plaques on dorsum of hands (gauntlet) and dorsum of feet (gaiter), butterfly rash over face, casal's necklace, mucosa-cheilitis, angular stomatitis, glossitis, half and half nails[5]	15 – 20 mg/day	Mild cases – nicotinic acid 50 mg TID orally If symptomatic, nicotinic acid 25 mg TID IV Advanced stages – nicotinic acid 50–100 mg IM TID × 3–4 days, followed by similar quantities PO
B6 (Pyridoxine)	Decarboxylation and transamination of amino acids, gluconeogenesis, conversion of tryptophan to niacin, sphingolipid synthesis, prostaglandin synthesis, neurotransmitter synthesis	Photodermatitis, angular stomatitis, glossitis, cheilitis	Adult 1. 2-1.5 mg per day; children 0.3-1.2 mg per day	Pyridoxine 50–100 mg/ day prevent neuropathy 100 mg/day IV in those with seizures
B9 (Folic acid)	Single-carbon transfers in amino acid, purine and pyrimidine metabolism	Glossitis with atrophy of the filiform papillae, angular cheilitis, mucosal ulceration, perirectal ulcerations, perineal	Adults - 400µg/day Children 80-300µg/day	Folate 1-5 mg/day followed by 1mg/day

		seborrheic dermatitis, diffuse brown hyperpigmentation concentrated in the palmar creases and flexures.		
Vitamin B12 (Cobalamin)	Methylcobalamin is a coenzyme for methyltransferase involved in DNA protein, and lipid metabolism 52-Adenosylcobalamin involved in fat and carbohydrate metabolism	Linear glossitis in early stage[6], Hunter's (or Moeller-Hunter) glossitis, angular chelitis, hairdepigmentation, cutaneous hyperpigmentation mimicking, Addison's disease, glossodynia, lingual paresthesia, xerostomia, stomatitis	2 to 3 µg per day	500-1000 µg administered via the i.m or s.c route for 5 to 10 days, followed by 100 to 200 µg per month
Biotin	Co-factor for carboxylating enzymes involved in fatty acid synthesis, lipogenesis and aminoacid catabolism	Erythematous, scaling and crusting dermatitis around eyes, nose, and mouth and periorificial, perianal region, alopecia, glossitis	Children: 5-20µg/day Adult: 25-30µg/day	Acquired deficiency: 150µg of biotin per day until resolution of symptoms
C (Ascorbic acid)	Cofactor in collagen biosynthesis, prostaglandin metabolism, fatty acid transport, and norepinephrine synthesis	Phrynoderma, cork screw hairs, woody edema of lower extremities, ecchymoses, poor wound healing, splinter hemorrhages, gingival swelling and bleeding	40 – 60 mg/day	Adults: 800 mg/day orally Children: 150 mg/day orally

Table IV. Deficiency of minerals

Minerals	Function	Cutaneous findings	Rda	Treatment
Iron	Heme synthesis, oxidation-reduction reactions, collagen synthesis	**Mucous membrane**: Angular stomatitis, aphthous stomatitis, glossodynia, atrophied tongue and papillae, blue sclera, pruritus **Nails** Fragile, longitudinally ridged lamellated brittle nails, thinning and flattening of nail plate, koilonychia **Hair** Lustreless, dry, split hair shaft, heterochromia of hair, hair loss[7]	Children:8-10mg/day Adult men: 8mg/day Adult women: 18mg/day Pregnant women: 27 mg/day	Ferrous salt 325 mg (65 mg of elemental iron) orally tds IV ferric carboxymaltose injection 15mg/kg body weight maximum of 750 mg on 2 occasions 7 days apart

Minerals	Function	Cutaneous findings	Rda	Treatment
Zinc	Essential component of many metalloenzymes, regulates DNA and RNA polymerases, ribonucleases, wound healing, immune regulation, collagen synthesis	Periorificial and acral dermatitis with sparing of upper lip, alopecia, dry and brittle hair, alternating light and dark bands[8], delayed wound healing	<6 months - 3mg 6months-1year -5 mg 1-7 years - 10 mg >7years - 16 mg Pregnancy and lactating women - 20-25 mg	Acrodermatitis enteropathica - 3mg/kg/day of elemental zinc Acquired zinc deficiency Children - 0.5-1mg/kg/day Adults - 15-30 mg/day
Copper	Stimulates profileration of keratinocytes and fibroblasts, helps in wound healing	Lax skin, wrinkles, accelerated aging, graying of hair, poor wound healing	Children-340ìgm/day Adults - 900ìgm/day Upper limit Children - 1000µgm/day Adults-10000µgm/day	Supplementation of copper in diet
Selenium	Essential component of glutathione peroxidase – an antioxidant	White nail beds, hypopigmentation of skin skin and hair (pseudoalbinism)	Children: 15-40 µg/day Adults: 55µg/day	2mg/kg/day
Manganese	Activates glycosyltransferases-synthesis of glycosaminoglycans and glycoproteins, metalloenzymes-Pyruvate carboxylase Superoxide dismutase, high concentration in melanocytes	Mild dermatitis, reddening of the hair, slow and nail growth, miliaria crystallina	Children: 0.6-1.6 mg/day Adults: 1.8-2.3 mg/day	
Sulphur	Essential component of methionine and cysteine - keratinization Chondroitin sulphate - formation of dermal collagen	Tissue paper scar Sparse fair hair Exfoliative psoriasis	800-900 mg/day	

Conclusion

Infants and children require sufficient calories and nutrients for normal growth and development. Malnutrition is one of the major causes of morbidity and premature death. Though pediatricians are veterans in managing emergency and improving general condition in malnourished children, it is important not to miss the cutaneous manifestation of malnutrition which may be the presenting sign in some cases. The key to diagnosis is in having a familiarity with the range of clinical presentations associated with these disorders and maintaining an appropriate index of suspicion for these disorders when evaluating dermatologic patients with skin findings or a history that might suggest a nutritional etiology. This article is to highlight the importance of detecting nutrition related disorders at the earliest by looking at the skin. The effective correction of nutritional profile ensures dermatological cure.

Points to Remember

- ***Skin can reflect nutritional deficiency.***
- ***Sound knowledge about dermatological manifestations of nutritional deficiency will help in early diagnosis.***
- ***Correction of the deficiency will reverse the cutaneous findings.***

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NEWS AND NOTES

ADOLESCON 2016

16th National Conference of Adolescent Health Academy IAP

Organizer: AHA & IAP AGRA Branch

Venue: Hotel 4 Points By Sheraton Fatehabad Road Agra

Date: 17 & 18 Sept, 2016

Registration Details

Category	Upto March 31	Upto May 31	Upto July 31	Upto Conference
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RADIOLOGY

THE ACUTELY SWOLLEN LIMB

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A common challenge in pediatric practice is to determine the cause of an acutely swollen limb. While bites and cutaneous infections are visualized on inspection, deeper causes cannot be readily ruled out. This is where imaging helps. The practical imaging modality useful in the initial stage of work-up is the plain X-ray. It is simple, quick, cheap and easily available. Intelligent observation of the various tissue planes in the body will provide a very helpful answer and give a direction for appropriate therapy.

A study of the plain X-ray of limb not only means a perusal of the bones but also of the soft tissue around the bones. Let us look at the various planes to be seen. The outer edge of the limb is the skin. Under the skin is the subcutaneous fat which is lucent compared to the deeper muscle. Deep to the white muscle is the dense white bone. The bone has an outer white cortex and an inner grey medulla. Remember always to image both limbs so that you can compare.

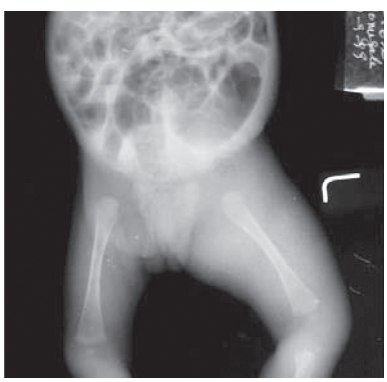

Fig.1. Acute osteomyelitis

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Fig.1 is an AP X-ray of both lower limbs. The right limb shows soft tissue planes of normal thickness. On the left side the subcutaneous fat is normal but there is thickening of the muscle plane. If you see carefully the muscle is swollen on both sides of the bone. So the muscle swelling is circumferential around the bone. Another feature is that the muscle swelling extends to the entire length of the bone. These two features constitute the 'muscle sign' and denote acute osteomyelitis. This sign is seen in about three days following infection of the marrow. The diagnosis of osteomyelitis is to be made at this stage when the suppurative process is well established and drilling into the medullary cavity will yield pus. The muscle sign is produced by the inflammation of muscle due to leakage of inflammatory exudate from the medullary cavity into the surrounding muscle through minute discontinuities in the periosteum. Although bone destruction is present at this stage it is not evident in the X-ray as atleast 30% to 50% bone loss is required before there are radiologically evident bone changes. Full blown bone destruction and periosteal reaction is seen in 7 to 10 days, by which time it is an irrevocable process associated with much morbidity.

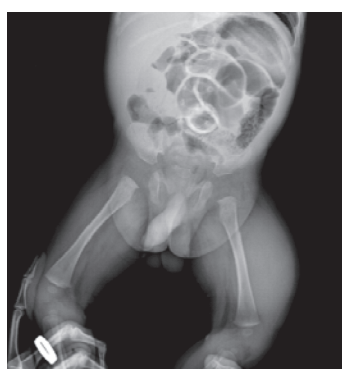

Fig.2. Deep abscess- left thigh

In Fig 2. there is soft tissue swelling within the muscle plane on the lateral aspect of left thigh. It is clearly different from the previous figure. The swelling is focal because it does not extend over the entire length of the bone and it is not seen on both sides of the bone. Thisis only a deep seated abscess and needs incision and drainage. Note that the subcutaneous fat is normal or thinned out.

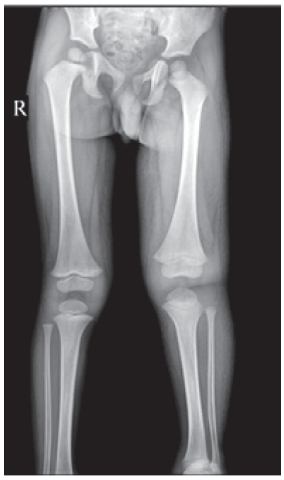

Fig.3. Cellulitis- left thigh

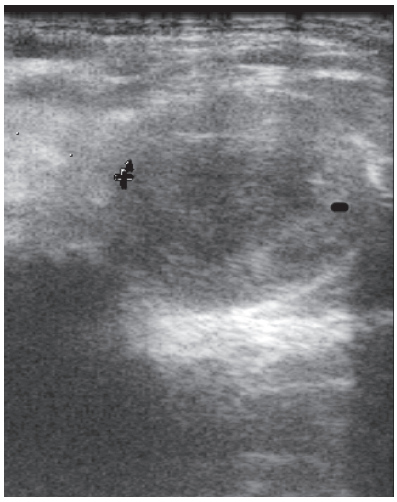

Fig.4. Ultrasound –abscess. (walled hypoechoic collection).

In Fig 3. there is thickening of the subcutaneous fat on the left. Note that the fat is also less lucent on the swollen side. Again it is always useful to compare with the other normal side.This is cellulitis, which can be quite confusing as it can overlap with other conditions. Diffuse cellulitis can sometimes be associated with a small occult abscess or lymphadenitis with or without suppuration. Ultrasound is very useful in these situations to look for enlarged nodes or a small pus collection (Fig.4) that can be accurately located and drained. Though rare in children, deep venous thrombosis presenting with a swollen limb can be diagnosed with Doppler ultrasound. There will be no blood flow in the affected vein which is distended with thrombus so that it is not compressible. Children with lymphedema can also present with cellulitis.

We have now seen how to intelligently scrutinize the various tissue planes in the simple plain X-ray of the limb to resolve some diagnostic dilemmas regarding the acutely swollen limb in a sick child.

NEWS AND NOTES

MAMALLA PEDICON 2016

41st Annual Conference of IAP-TNSC

Organised by

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Indian Academy of Pediatrics - Chennai City Branch (IAP-CCB)

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CASE REPORT

FETAL CHOLELITHIASIS – A FOLLOW UP

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*****Vindyarani WK**

Abstract: *Fetal gallstones, detected by routine third trimester ultrasound, have been described in the literature with controversial clinical significance. We report a case of fetal cholelithiasis detected at 38 weeks gestation during a routine scan. The patient remained asymptomaic and had a complete spontaneous resolution of the gallstones in postnatal life as described in most other studies.*

Keywords: *Fetal cholelithiasis, Follow up, Ultrasonogram*

Fetal gall stones are extremely rare. Most of them resolve spontaneously prior to delivery. The prevalence of neonatal gallstone is 0.13% to 1.5%[1]. The frequency of diagnosis has increased over the last few years, probably due to the increasing use of ultrasound examination in clinical practice. However, there is not much of information from India. The purpose of this case report and review is to increase awareness about the management of gallstones in children. Here, we present the sonographic findings and neonatal outcome in a fetus presented with multiple gallstones.

Case Report

Mother was 28 years at conception. It was her first spontaneous conception; she had all her regular antenatal checkups in other centres. She was not having any chronic medical illness and there was no history of diabetes mellitus, pregnancy induced hypertension or bleeding per vagina. She took iron/folic acid and calcium tablets during antenatal period. Blood investigations done were normal. She underwent 3 antenatal ultrasounds - one in the first trimester showed a single viable intrauterine fetus. Anomaly scan done at 20 weeks was normal.

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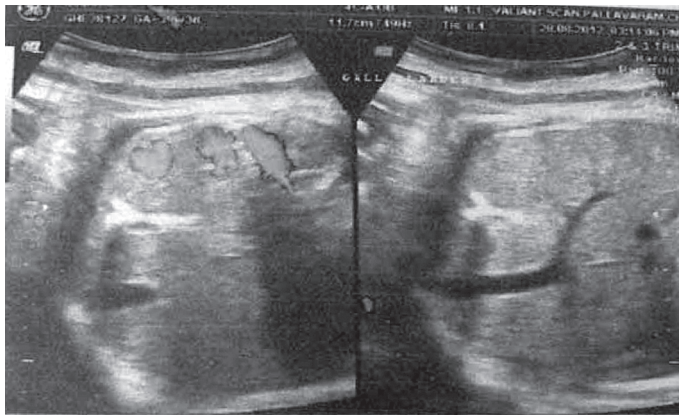

Fig.1. USG at 38 weeks of gestation showing multiple gall baldder stones

Third trimester scan done at 38 weeks showed multiple small, well defined hyperechoic lesions in the gall bladder consistent with cholelithiasis (Fig.1).

Cesarean section was performed at term in view of obstetric indication and delivered a female baby weighing 3250 gms at birth with Apgar score of 8 at one minute and 9/10 at 5 minutes. Baby passed meconium within 24 hours of life and was taking feeds well. Her postnatal examination was unremarkable.

Complete blood count, peripheral smear, reticulocyte count and liver function tests were within normal limit for the age. Blood group of the baby was A+ve (Mother B+ve). As earlier literature showed that >90% of fetal and neonatal gall stones were self limiting which do not warrant any aggressive approach unless it is associated with strictures or anatomic abnormalities of the common bile duct[1], we decided to keep the baby under follow up. Ultrasound abdomen done at 10 days of life and at 1 month showed persistence of the stones (Fig.2a and b).

Patient was lost for follow up between 1 and 6 months due to personal reasons. USG done during follow-up at 6 months of age was normal with complete resolution of the stones (Fig.3).

Discussion

Despite many obstetric ultrasound examinations performed annually world-wide, fetal cholelithiasis has been an extremely rare finding. Brown, et al reported fetal

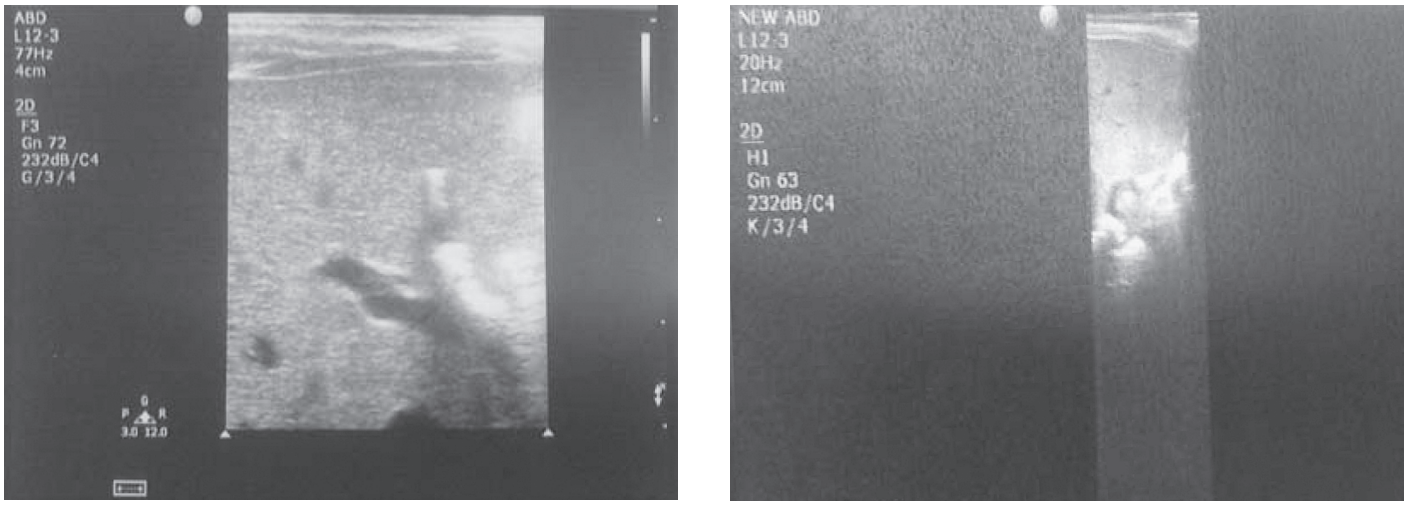

Fig.2a&b USG at 10 days and 1 month of postnatal life showing mutiple stones in gallbladder

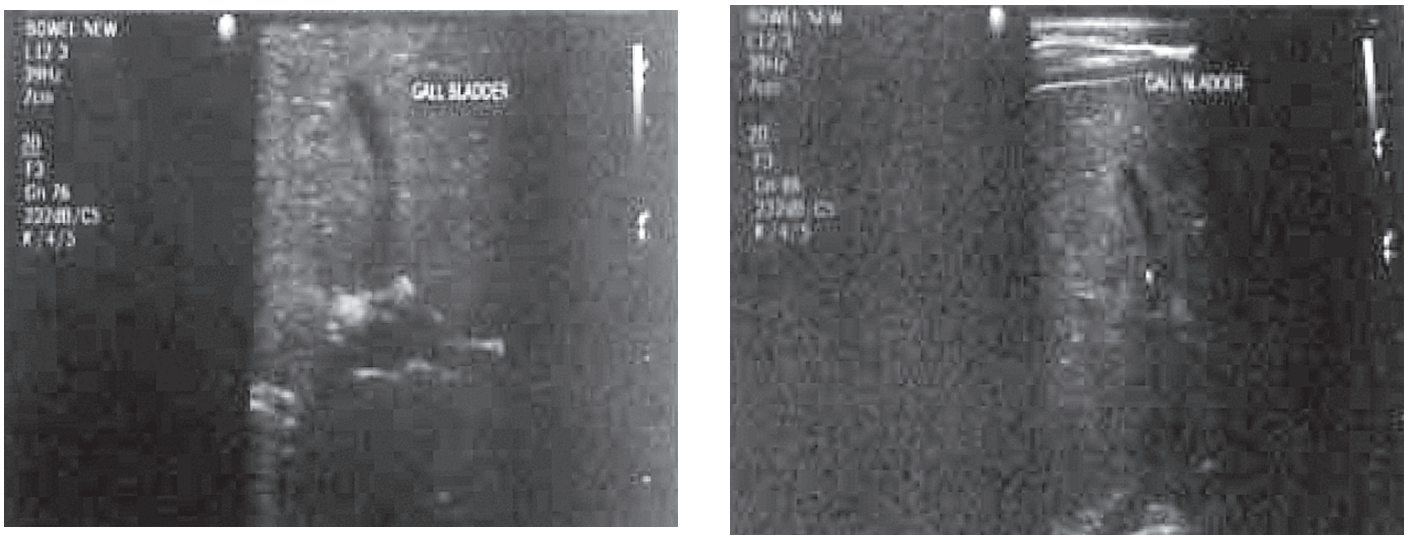

Fig.3. USG at 6 months of age with not a single stone in gall bladder

Table I. Causes of fetal cholelithiasis

Maternal	Fetal
Placental abruption	Rhesus or ABO blood group incompatibility
Increased estrogen levels	Idiopathic
Narcotics use	Congenital anomalies (cardiovascular, gastrointestinal, urinary
Prolonged fast	Twin pregnancy with fetal demise of one twin
Diabetes of any type	Genetic anomalies (trisomy 21)
	Growth restriction
Pharmacological treatment (ceftriaxone, furosemide, prostaglandin E2	Hepatitis

gallstones in 26 patients.[1] Echogenic material in the gallbladder was observed only in third trimester fetuses as in our case and resolved spontaneously in the majority.[1] No predisposing risk factors were identified in any of these series. In 12% of fetuses there were single echogenic focus, 73% showed multiple foci and the remaining 15% showed diffuse filling of the lumen of the gallbladder. A review of 30 cases of fetal cholelithiasis by Suchet, et al with a long-term follow-up in 21 out of 30 only 3 patients, a persistent echogenic material in the gallbladder after 2 weeks of life was observed without any abdominal symptoms.[2] Stringer, et al reported a series of 3 male fetuses examined sonographically in late gestation with evidence of gallbladder cholelithiasis.[3] In 2 of these, the abnormalities noted sonographically resolved spontaneously in 6 weeks, while in the third, a persistent gallbladder "calculus" until 6 months been observed.

The differential diagnosis of fetal gallstones in USG includes single or multiple calcifications within the fetal liver.[4,5] Correct identification of fetal gallstones allows adequate counseling and avoids unnecessary work-up and maternal anxiety.

Two major theories in the formation of fetal gallstones have been proposed:

1. The presence of a placental hematoma with subsequent breakdown of hemoglobin to bilirubin and 2. Increased cholesterol secretions and depressed bile acid synthesis caused by estrogens.[6,7]

The common causes for fetal cholelithiasis are enlisted in Table I.

The natural history of fetal gallstones is one of the following in most of the cases [1]

1. Spontaneous passage of the gallstones during early neonatal period or
2. The dilution of cholesterol crystals with postnatal hydration

Most neonates have spontaneous passage of gallstones. It can cause neonatal cholecystitis, stones in common bile duct and peritonitis in rare instances. Hence, a follow up is required with clinical correlation and sonography. If symptomatic then, ursodeoxycholic acid: 10-15 mg /kg / day can be used.[10]

Conclusion

In conclusion, attention has to be reserved for potential maternal or fetal risk factors. A close follow-up is indicated in these patients until spontaneous resolution is demonstrated by traditional ultrasound. Several questions remain unanswered about the etiology and the risks of further gallstone formation in cholelithiasis detected during pregnancy. With available evidence we can conclude that most cases of fetal gallstones are asymptomatic and resolve spontaneously without specific intervention.[1,8,9]

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- The Life Members of Indian Academy of Pediatrics from Delhi State are eligible to apply for this post.
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- The candidate should send his / her biodata in not more than 400 words along with his / her nomination.
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