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In Memoriam

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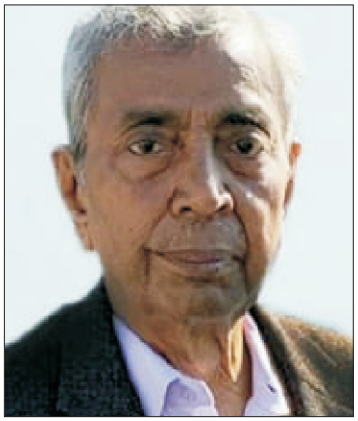

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Issues and challenges in the development of COVID-19 vaccines

There could be various scenarios once the COVID-19 vaccines are available. The most-favorable scenario would be that the efficacy trials of many candidate vaccines will yield good results and provide robust protection against the COVID-19. In that scenario, the vaccines that can be rapidly produced in bulk amount (e.g. mRNA, DNA, adenovirus vectors) shall be the first choice. Another situation may emerge where a nucleic acid-based (mRNA vaccine) vaccine work better if boosted by an inactivated vaccine. The most devastating scenario would be if any of the vaccines aggravates the disease in the recipients who get infected with SARS-CoV-2. This situation will bevery damaging to the whole effort of vaccine development. The mission of an effective SARS-CoV-2 vaccine poses challenges that need to be sorted out.

Antigenic type

Based on the antigenic structure of Coronavirus targeting the 'S' glycoprotein in vaccine development could be ideal. But at the same time it has to be considered the other antigens. The 'N' protein is more conserved between SARS-CoV-1 and MERS-CoV strains and induces a good long-lasting memory T-cells in humans. 'N' protein can be a potentially viable addition to accord cross-protective and long-lasting T-cell immunity. Also a dimeric form of MERS-CoV RBD can be targeted as a more effective immunogen. Experts have expressed the need for having more than one antigen for better immunogenicity.

SARS-CoV-2 is a single-stranded RNA virus, prone to mutate frequently. One mutation in the 'S' gene has been identified leading to two lineages of the virus: "L type" and "S-type". Hence similar to influenza vaccine, there may arise to periodically update the vaccine formulation in the future.

Immune enhancement

Rarely the disease runs a more severe course paradoxically in individuals who are vaccinated. There are two immune-mediated mechanisms. An Ab-dependent enhancement (ADE), where there is increased binding efficiency of virus-antibody complexes which triggers viral entry. The second one is 'vaccine-associated enhanced respiratory disease' (VAERD). This may happen because the vaccines contained conformationally incorrect antigens.

Route of administration

Route of administration of a vaccine can impact its effectiveness. Continuing with the conventional and most widely practiced intramuscular route, most of the candidate vaccines have been tried with intramuscular route only. It has been seen that employing an intranasal route for vaccination induces humoral and cellular responses in the respiratory tract leading to higher protection levels.

Duration of immunity and the need for boosting

Waning of immune responses is known with most coronavirus infections. The common-cold coronaviruses provide immunity that lasts only a few weeks to months. The studies done on individuals recovered from SARS-CoV-1 in 2003-04 show that the antibodies are detectable until about 2 years after recovery. However, T-cell-based immunity lasts at least until 6 years. Knowledge on durability of the immunity after natural infection with SARS-CoV-2 is incomplete.

Further studies will be needed to fully dissect immunological memory responses, their durability, and their contribution to long-term protection reinfection. The precise understanding of the Ab dynamics and the duration of immunity induced by the candidate vaccines will be of paramount significance in ascertaining the need for the booster doses of the vaccines.

'Endpoint' for assessing efficacy

There is much debate on what should be the ideal 'primary endpoint' to demonstrate the effectiveness of a SARS-CoV-2 vaccine. It could be either protection from the infection (sterilizing immunity) or attenuation of the disease severity.

Dosing issues

For any vaccine the key issue is the correct identification of dose that best balances efficacy and safety. The SARS-CoV-2 is more lethal in the elderly age-group and in those with co-morbidities. However, the immune response in these populations is generally suboptimal as compared to young healthy individuals, thus requiring a higher dose. This poses another challenge to the ongoing efficacy trials of SARS-CoV-2 vaccines. Striking the right balance is the key issue.

Fear and concern about COVID-19 vaccines

Misinformation, non-scientific social media posts and taboo are part of any new vaccine idea. Since the beginning of the COVID-19 pandemic, there have been much misinformation and even conspiracy theories. All these have the potential to reduce vaccine uptake.

As a positive move, WHO recommends a preemptive provaccination strategy that psychologically inoculates the population and maximizes uptake of vaccines.

Post-licensure challenges

There are bound to be challenges to the use of an effective SARS-CoV-2 vaccine even after the vaccine is licensed. Also there are other challenges ahead of large scale introductions of an effective vaccine. Many vaccine candidates are being developed by manufacturers that have never developed and launched a vaccine to market. Technologies that have never resulted in a licensed vaccine are being explored. Billions of doses of the vaccine would be required soon after it is licensed would be beyond the capability of most vaccine manufacturers. This could bring up unforeseen issues in logistics and consequent delays. The initial aim is to have at least two billion doses available by the end of 2021, to protect high risk and vulnerable people and frontline healthcare workers.

Equitable distribution of the vaccines so that it is accessible to those who need it the most would be a significant challenge. Serious planning at the global and country-level has already been started to tackle this challenge suitably.

The way forward

The challenge is not only to develop safe and effective COVID-19 vaccines but also the equitable distribution. WHO in collaboration with GAVI, the vaccine alliance, and Coalition for Epidemic Preparedness Innovations (CEPI) has initiated a unique global collaboration, known as 'COVAX', a COVID-19 Vaccines Global Access facility. COVAX plans to pool economic resources to achieve vaccine developers to make high-risk investments for the development of vaccines and subsidize costs for middle-and low-income countries.

Sustained global collaboration, public support, and technological advancements would boost the pandemic vaccine enterprise during this unprecedented crisis. Optimism is crucial to move forward, but nothing can be achieved without a strong and sustained coordination among the various sectors.

Dr Jaydeep Choudhury
Editor-in-Chief

Management of Status Epilepticus in Children

Mihir Sarkar
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Objectives

1. Definition and classification of status epilepticus
2. Importance initial assessment and stabilization
3. Time bound algorithmic approach of management of status epilepticus
4. Basics of pharmacotherapy of anti epileptic drugs for status epilepticus
5. Role of continuous EEG (cEEG) and amplitude integrated EEG(aEEG)
6. Weaning of Intravenous anti epileptic Drugs.

Introduction

Status epilepticus (SE) is the most common acute life threatening neurological emergency in children which require prompt stabilization and targeted treatment to reduce mortality and adverse neurological sequelae. It has an annual incidence of 17–23 cases per 100,000 children per year, with 22% of patients requiring Intensive Care Unit (ICU) admission. Reported mortality ranges from 3-5% after pediatric Convulsive Status Epilepticus (CSE) and neurological sequelae occur in up to 34% of children.

Definition of SE

Definition of status epilepticus has evolved over time.

Status epilepticus (SE) :

A seizure lasting more than 30 minutes or recurrent seizures for more than 30 minutes during which the patient does not regain consciousness.

Operational definition :

SE was defined as 5 min or more of (i) continuous clinical and/or electrographic seizure activity or (ii) recurrent seizure activity without recovery (returning to baseline) between seizures.

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Rationale of operational definition – Urgency to achieve seizure termination and avoid consequences.

1. Seizures that last longer than 5 minutes often do not stop spontaneously.
2. Permanent neurological injury and resistance to anti epileptic drugs(AED) can occur before 30 minutes of seizure.

Classification of SE

Convulsive status epilepticus (CSE) :

Defined as convulsions those are associated with rhythmic jerking of the extremities.

Non-convulsive status epilepticus (NCSE) :

Defined as seizure activity seen on electroencephalogram (EEG) without clinical findings associated with CSE.

In intensive care setting it usually follows uncontrolled CSE or acute brain injury with impaired mental status. Some form of subtle motor movement like rhythmic muscle twitches or tonic eye deviation can occur. Mortality may increase upto 85% if NCSE persisted for prolonged duration (>20 hour). Continuous EEG monitoring is needed to pick up prolong NCSE and titrate anti epileptic drugs.

Refractory SE (RSE) :

Continuation of either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) is considered refractory.

The mortality rate in children with RSE may be 20% in symptomatic RSE and 4 % in idiopathic RSE. Return to functional baseline is more likely for SE patients than for RSE patients. Post-SE epilepsy may be seen more frequently in long-term survivors with RSE than in those with non-refractory SE.

Potential underlying etiology

Acute processes :

1. Prolonged febrile seizures are the most frequent cause of SE in children. Account for up to 35% of all episodes of SE.
2. Metabolic disturbances: Electrolyte abnormalities, hypoglycemia, inborn error of metabolism, renal failure
3. Central nervous system infection: Meningitis, encephalitis, abscess
4. Stroke: Ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, cerebral sinus thrombosis
5. Head trauma with or without epidural or subdural hematoma
6. Drug toxicity
7. Non-compliance with AEDs
8. Hypoxia, cardiac arrest
9. Hypertensive encephalopathy, posterior reversible encephalopathy syndrome
10. Autoimmune encephalitis (i.e., anti-NMDA receptor antibodies, anti-VGKC complex antibodies), paraneoplastic syndromes

Chronic processes :

1. Preexisting epilepsy: breakthrough seizures or discontinuation of AEDs
2. CNS tumors

Management goal

Emergent cessation of clinical and electrographic seizure in time bound manner.

Strategies of management :

1. Assessment and stabilization of Airway, Breathing and Circulation.
2. Stop seizure – Anti epileptic drug treatment
3. Immediate treatment of reversible causes like hypoglycemia, dyselectrolytemias, raised intracranial pressure.
4. Screening for underlying cause of SE.
5. Prevent complications.

Refractory status epilepticus management in PICU

If the seizure continues (clinical or electrographic) after administration of a benzodiazepine and another appropriately dosed anti-seizure medication, then the patient meets criteria for refractory status epilepticus. The algorithm of management of status epilepticus in emergency department (in accordance of American Epilepsy Society Guideline) is shown in Fig 1 and simultaneous assessment and management of associated life threatening events shoen in table 1.

T*herapeutic objectives in RSE :*

1. Abort clinical and electroencephalographic epileptic activity
2. Neuroprotection
3. Avoid and treat systemic complications of coma and prolonged sedation.

General measures :

Evaluate need for

- Airway support
- Central venous access and/or arterial access
- Vasoactive support
- Temperature control

Any additional diagnostic testing or procedures, including but not limited to:

- Lumbar puncture
- Laboratory workup including blood glucose checks
- Neuro checks every 1 hour
- Imaging (CT or MRI)

Treatment

At present, there is a lack of sufficient high-quality evidence to recommend a uniform management strategy for RSE. The main decision point at this step is to consider repeat bolus of the urgent control of AED or to immediately initiate continuous infusion of anesthetic agent. Treatment algorithm of refractory status epilepticus shown in Fig 2.

Decision depends on :

1. Availability of pediatric intensive care facility
2. Convulsive vs nonconvulsive status
3. Maintainability of airway
4. Hemodynamic stability.

The recommend proceeding is to start with additional continuous infusion of anesthetic agent immediately, in combination with critical care treatment. Comparative evidence to recommend one of these anesthetic drugs over another is insufficient, so drug

Fig 1. Algorithm of Management of Status Epilepticus in Emergency Department (in accordance to American Epilepsy Society Guideline)

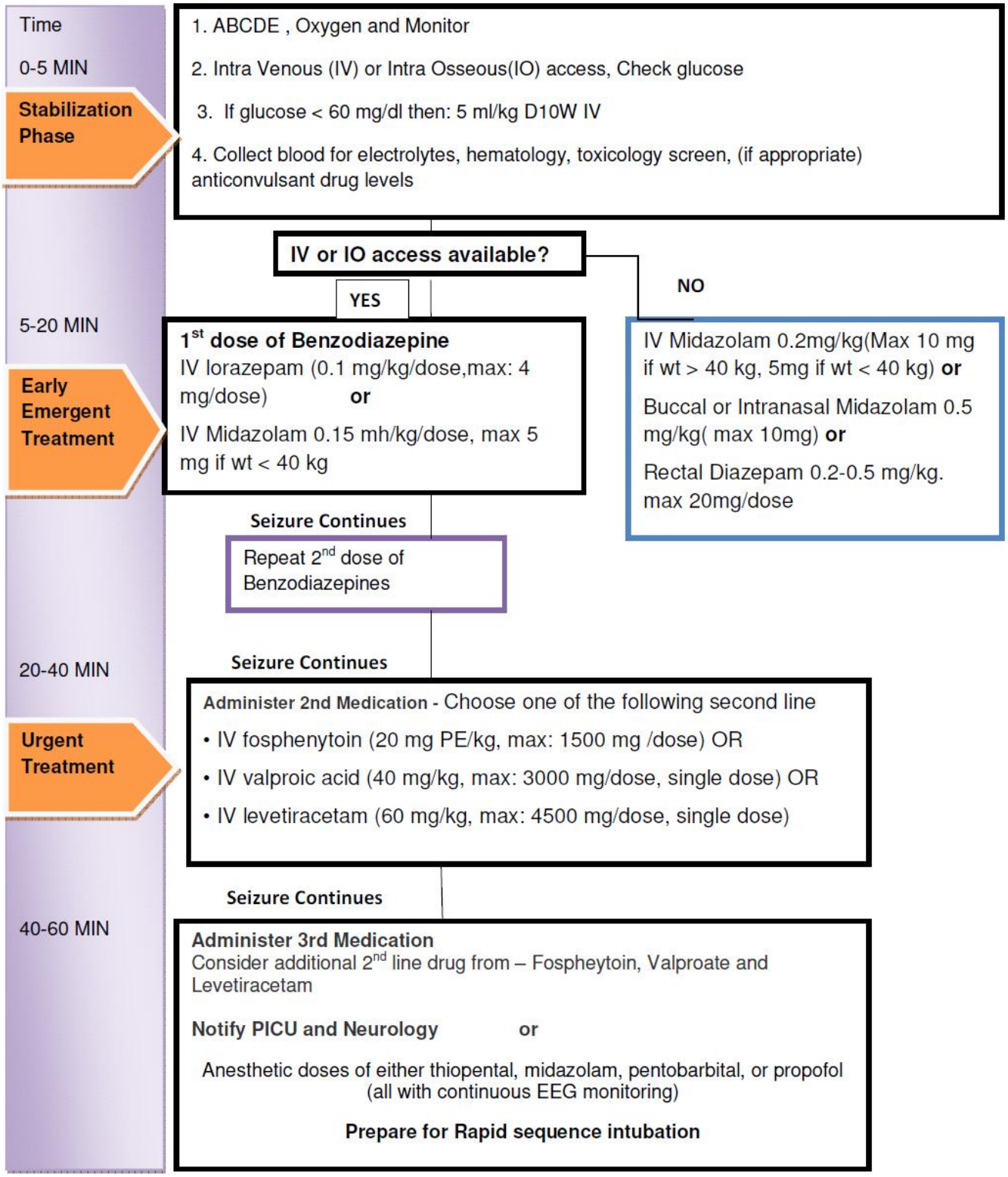

Table 1. Simultaneous Assessment and Management of Associated Life Threatening Events. Concurrent assessment, reassessment and management should occur in emergency and intensive care unit if seizure activity is continuing.

System	Assessment	Intervention
AIRWAY	Airway compromise – - Secretion and trismus - Snoring or Gurgling	• Non-invasive airway protection and • Gas exchange with head positioning, Jaw thurst, keep the child in recovery position. Maintain airway patency
	Complete airway obstruction Persistent alteration of mental status Need of Anesthetic drugs	• Intubation (if airway/gas exchange compromised or elevated ICP suspected)
BREATHING	Perioral cyanosis, Low O2 Saturation	• Apply Oxygen with Non rebreathing mask(NRM) or Mechanical Ventilation if gas exchange compromised
CIRCULATION	Tachycardia with poor peripheral perfusion	• Monitor HR, BP, CRT, Urine out put • Peripheral IV access. Send blood sample • Fluid resuscitation with Normal Saline • Maintenance - Dextrose normal saline (DNS) or normal saline according to the glycemic status.
	Hypotensive shock	Vasopressor support Maintain blood pressure in the normal range.
DISABILITY	Check finger prick blood Glucose	If glucose < 60 mg/dl then 5 ml/kg D10W IV
	Correct Hyponatremia carefully	Increase sodium to 120 mEq/L quickly then slowly increase by less than 8-12 mEq/L/day to mitigate risk of cerebral pontine demyelination.
	Quick neurological Assessment Level of Consciousness - GCS Presence of Subtle motor movements.	Limb Tone Pupil Deviation of eyes Response to Pain
	Raised Intracranial Pressure (ICP)	**Neuroprotective strategies** - Target normocapnea (PaCO2 35-40) and normoxia (SpO2 90-99%). Target normal BP for age. Avoid hypotension. Assure adequate intravascular volume. Target normothermia (36C-37.5C). Head end of Bed at 30^{o} Maintain normal Blood Glucose- **Osmotherapy to reduce ICP** – 3% NaCl preferred. Helps to prevent hypotension. Maintain Na – 145-155 meq/l .
	Relevant History	Onset of Seizure Focal onset ? Pre-hospital treatment or any chronic treatment Previous successful hospital treatment.
EXPOSOURE	Toxin Trauma	Relevant history of drug intake or toxin Decontamination measures Antidote if available Cervical spine should be immobilized if trauma is suspected.

selection is based on the advantages and side effect profile of each, with consideration of each patient's comorbidities and possible complications of the therapies. Use of valproate sodium, levetiracetam, and phenytoin/fosphenytoin in intermittent boluses may be considered if they have not previously been administered, particularly for patients with NCSE who are haemodynamically stable and have not required intubation. Pharmacology of anti epileptic drugs are shown in Table 2.

Super-refractory status epilepticus:

SE that continues 24 hours or more after the onset of anesthesia, including those cases in which status epilepticus recurs on the reduction or withdrawal of anesthesia.

NORSE:

New onset of refractory SE without a clear acute or active structural, toxic, or metabolic cause in a patient without active epilepsy or other preexisting relevant neurological disorder. It is a clinical presentation and not a specific diagnosis.

Febrile Infection related encephalopathy syndrome (FIRES):

NORSE with a prior febrile infection between 2 weeks and 24 hours prior to onset of refractory SE, with or without fever at the actual onset of SE.

Fig 2. Treatment Algorithm Refractory Status Epilepticus

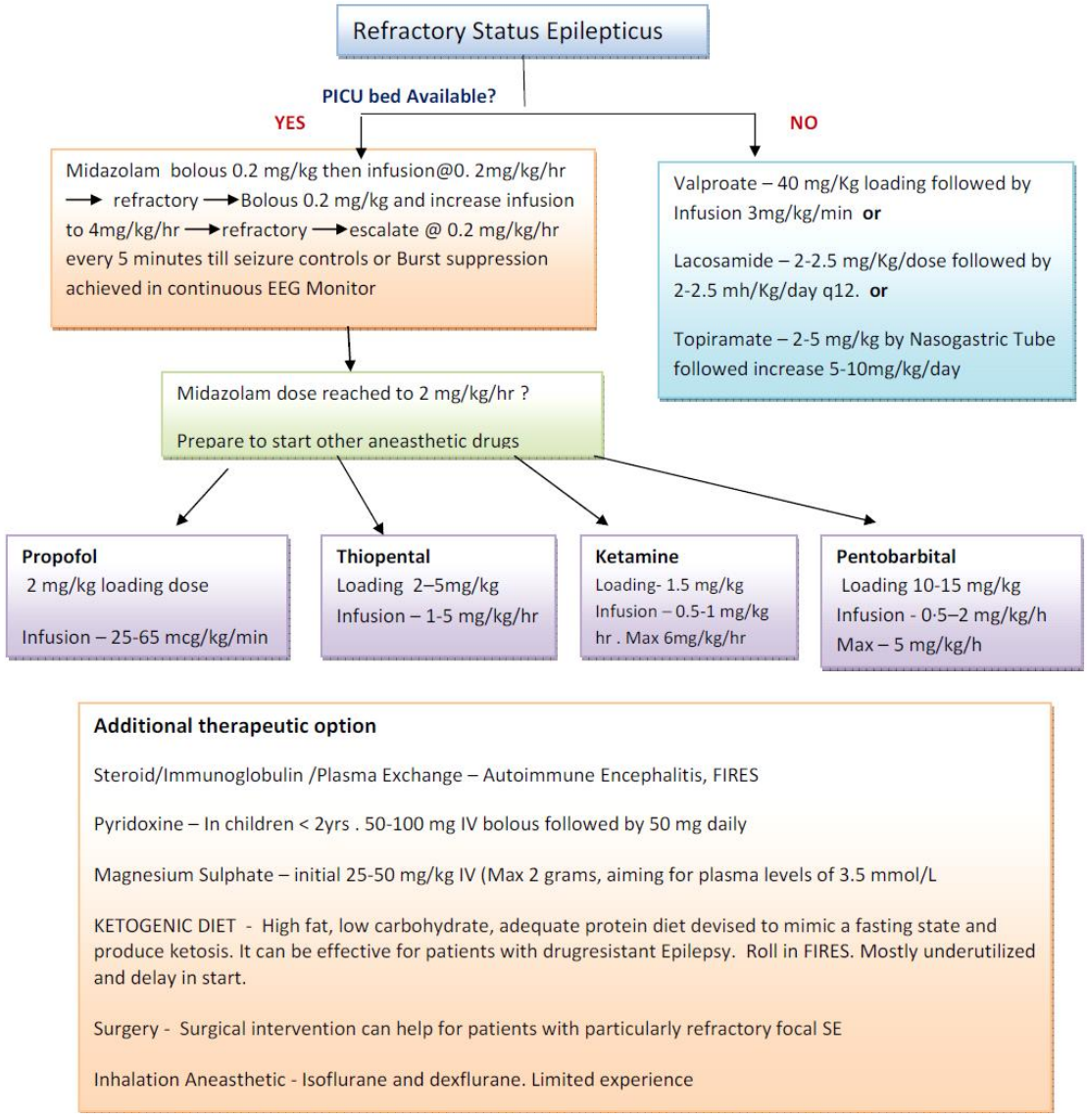

Table 2. Pharmacology of Anti Epileptic Drugs

Drug Name	Drug doses	Comments
Lorazepam	0.1 mg/Kg/IV (max 4 mg) @ 2 mg/min	Long acting benzodiazepine, Side effects: sedation, respiratory depression and hypotension.
Midazolam	0.15-0.2 mg/Kg;/IV or IM (Max 5 mg) Can be used by IM route. Buccal/Nasal: 0.2 - 0.3 mg/Kg (Max 5 mg)	
Phenytoin	20 mg/Kg (Max: 1000 mg) in NS @ 1 mg/Kg/min (Max 50 mg per min)	Must be diluted in saline. Side effects include; hypotension, cardiac arrythmias, 'purple glove syndrome', skin rashes. Contraindicated in severe hypotension and grade II AV block.
Fosphenytoin	20 PE/Kg, Rate: 3 PE/Kg/min	Fewer side effects compared with phenytoin. Can be given IM.
Valproate	20 mg/Kg-IV infusion over 15 min, max rate- 6 mg/Kg/min. Followed. an infusion of 1-2 mg/Kg/h	Avoid in presence of liver disease, coagulopathy, by thrombocytopenia, suspected metabolic disease, and in infants. 2nd line drug of choice in patient was on Valproate maintenance.
Levetiracetam	20-30 mg/Kg, over 15 min	Considered safe in children with metabolic diseases, oncology patients, and in those with liver disease or coagulopathy.
Lacosamide	2-2.5 mg/Kg/dose followed by 2-2.5 mh/Kg/day q12.	Minimal drug interactions Adverse effect rare -except mild hypotension
Topiramate	Initial dose: 5-10 mg/Kg/day orally, maintenance dose of 5 mg/Kg/day, if effective	Side effects: metabolic acidosis, decreased sweating and glaucoma
Thiopentone	Induction: 3 mg/Kg bolus, repeated after 2 min, followed by maintenance 1-5 mg/Kg/hr (increasing 1 mg/Kg/hr every 2 min) to , control seizures and/or to achieve . "suppression-burst" EEG activity	Causes respiratory depression. Can also induce hypotension and heart failure, associated with an increased rate of nosocomial infections. Contraindicated in the presence of hypotension cardiogenic shock and sepsis
Propofol	2 mg/kg loading dose, Infusion – 25-65 mcg/kg/min	Hypotension, **Propofol infusion syndrome** – Metabolic acidosis, renal impairment, hypotension, Infusion duration should be as short as possible. Serial blood gas monitoring may be helpful to indentify metabolic acidosis early.
Pentobarbitol	loading 10-15 mg/kg infusion - 0·5–2 mg/kg/h. Max – 5 mg/kg/hr	Hypotension, Respiratory depression Cardiac depression Paralytic ileus, at high doses, complete loss of neurological function
Ketamine	Loading- 1.5 mg/kg Infusion – 0.5- 1 mg/kg hr . Max – 6mg/kg/hr	Noncompetitive NMDA receptor antagonist . Early use may be advantageous Should not be used ins intracranial mass lesion

Investigations

The steps included in the diagnostic work-up should be completed as soon as possible and occur simultaneously and in parallel with treatment.

All patients first line investigation

1. Fingerstick glucose
2. Monitor vital signs.
3. Head computed tomography (CT) scan (appropriate for most cases)
4. Order laboratory test: blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, AED levels if indicated.
5. Continuous electroencephalograph (EEG) monitoring

Consider based on clinical presentation

1. Brain magnetic resonance imaging (MRI)
2. Lumbar puncture (LP)
3. Comprehensive toxicology panel including toxins that frequently cause seizures (i.e. isoniazid, tricyclic antidepressants, theophylline, sympathomimetics, organophosphates, and cyclosporine)
4. Other laboratory tests: Liver function tests, coagulation studies, arterial blood gas, AED levels, toxicology screen (urine and blood), and inborn errors of metabolism
5. Work-up for autoimmune encephalitis: Anti-NMDA receptor antibodies, anti-VGKC complex antibodies and anti TPO antibodies.

Neuroimaging :

- Should be done, if feasible, in all children with SE, in whom no definitive etiology has been found.
- Only after the child is appropriately stabilized and the seizure activity controlled.
- Emergent neuroimaging for new-onset focal deficits/ persistent altered awareness/ fever /recent trauma,/history of anticoagulation
- Identify structural causes for SE
- Especially to exclude the need for neurosurgical intervention in children with new-onset SE without a prior history of epilepsy, or in those with persistent SE despite appropriate treatment.
- MRI is more sensitive and specific than CT scanning, but CT is more widely available and quicker in an emergency setting.

Electroencephalogram (EEG) :

Electroencephalogram is the graphical presentation of electrical activity originating from the neurons located predominantly in the outermost layers of the cerebral cortex, and observed via scalp electrical potentials.

Ictal EEG – EEG recording during seizure

Inter-ictal EEG – EEG recording between seizures.

Placement of electrodes on scalp –

What is the 10-20 system?

- An internationally recognized method that allows EEG electrode placement to be standardised.
- Ensures inter-electrode spacing is equal
- Electrode placements proportional to skull size and shape.
- Measures distance from readily indentified landmarks on head and place the electrodes at 10 percent or 20 percent of that distance in anterior, posterior or transverse direction.

Electrode placement for International 10-20 system shown in Fig 3.

Covers all brain regions – F = Frontal T = Temporal P = Parietal O = Occipital

Numbering system – Odd = left side, Even = right side, Z = midline

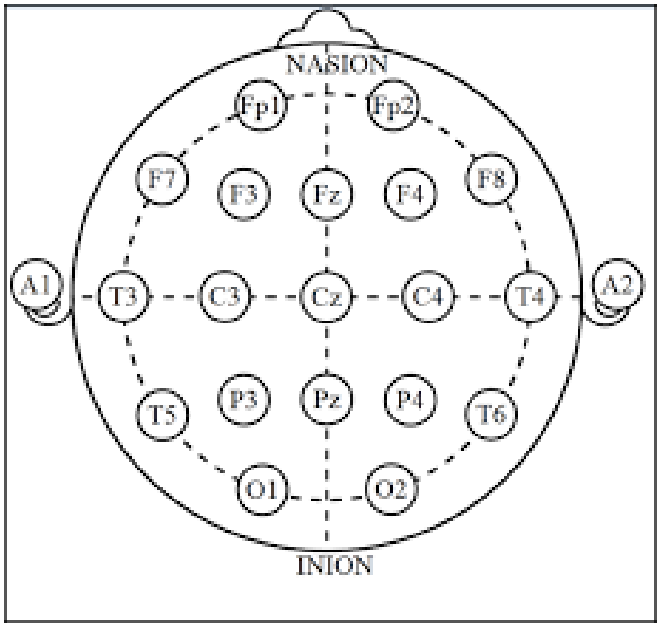

Fig 3. Electrode placement for International 10-20 system.

Epileptiform discharge (IEDs) patterns –

1. Spike (<70 µsec duration),
2. Spike and wave, or
3. Sharp-wave (70–200 µsec duration)
4. Polyspikes – multiple repetitive spikes occurring at 20 HZ .

Epileptiform Discharge – diagram and terminology shown in Fig 4.

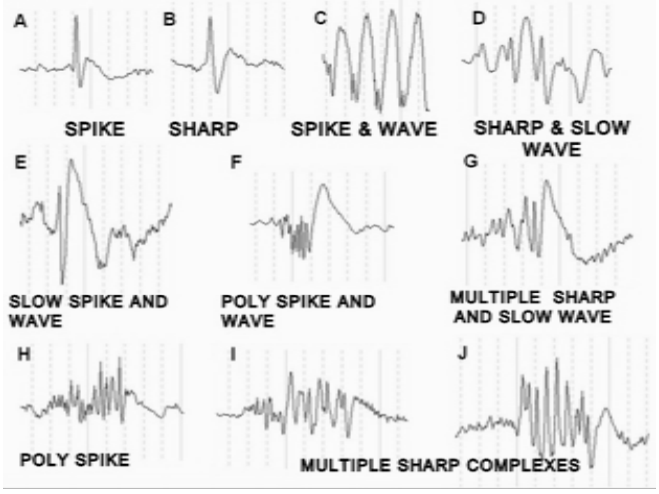

Fig 4. Epileptiform Discharge – diagram and terminology

Continuous EEG monitoring

In most of the clinical circumstances routine interictal EEG is done for maximum duration of 1 hour. Use of continuous 24 hours EEG or video-EEG is increasing in ICU to noninvasively monitor patients with RSE, traumatic brain injury, metabolic encephalopathy. It requires special expert team to set up the equipments, patients and to interpret the tracing. The PICU staff should be taught to identify seizures and patterns of interest.

When to order continuous EEG?

An EEG should be ordered after failure of the second-line agent or if the patient is paralyzed before clinical seizure activity stops (eg. For rapid sequence intubation).

What are the purposes of monitoring Continuous EEG in Refractory status Epilepticus?

1. Identification of NCSE – Nonconvulsive seizures and NCSE are common after apparently successful treatment of clinical seizures and status epilepticus.
2. Monitor the efficacy of continuous intravenous antiseizure drugs such as midazolam, propofol, or pentobarbital, for seizure suppression, burst suppression, or complete EEG suppression.
3. Monitor the adequacy of burst suppression (duration of burst and interburst periods) or complete EEG suppression induced by antiseizure drugs.
4. Recurrence of altered consciousness in a patient with known NCS should prompt consideration of repeat CEEG to exclude recurrent NCS.

When to worry about the continuous electroencephalography pattern?

1. Frequent repetitive electrographic seizures and repetitive generalized or focal epileptiform discharges of greater than 3Hz.
2. Repetitive or periodic epileptiform discharges less than 3Hz, if associated with an improved clinical response with repeated short treatment with a benzodiazepine.
3. Without a clear response, such EEG patterns fall along the ictal-interictal continuum without clear indication or consensus for continued treatment.

Assessment of efficacy of therapy for seizures and status epilepticus

Continuous EEG (cEEG) is required to help achieve treatment goals of seizure freedom versus the burst suppression pattern after IVAD administration is initiated.

Burst suppression is usually considered as a target for the titration of barbiturate or anesthetic treatment. But it is arbitrary. The optimal extent of burst suppression is not known. Burst suppression and more profound anesthesia can be difficult to achieve.

What is burst suppression?

Continuous alternation between high-voltage slow waves (occasionally sharp waves) and suppressed (< 10µV) electrographic activity.(Figure 3)

What is the optimum duration of burst suppression?

Usual recommendation – To maintain burst suppression patterns for 24-48 hours of clinical and electrographic freedom from seizure.

Fallacies of burst suppression:

1. Difficult to achieve
2. State of profound anesthesia leading to hypotension
3. No association with recurrence of seizure after

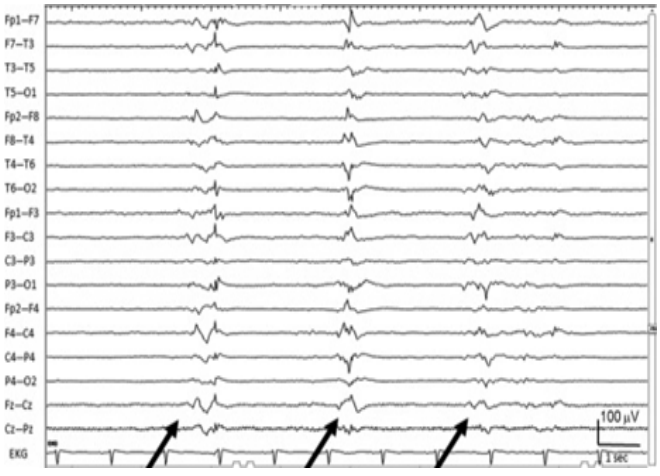

Fig 3. Burst Suppression in EEG

drug withdrawal

4. No correlation with functional outcome or mortality.

Limitations of continuous EEG monitoring

Not available in most of the secondary and many tertiary care centers in India.

1. Involve high level of expertise for data interpretation. Full review and analysis usually require a neurophysiologist or neurologist.
2. Application and maintenance of electrodes requires trained technologists
3. Interpretation is time consuming but has been reduced by technologic advances in digital acquisition, the use of spike- and seizure-detection algorithms
4. Automatic detection software is error prone
5. It is expensive, and access to equipment is variable
6. Delays in analysis reduce the benefits of anticipatory care
7. Scalp breakdown due to prolonged electrode placement.

Is there any alternative of continuous EEG monitoring ?

Amplitude-integrated electroencephalography (aEEG) – It is a bedside neurophysiology tool that uses a limited number of channels(2-4 channels) to record raw EEG signal that is then filtered, rectified, processed, and displayed on a semilogarithmic amplitude and time-compressed scale. It has been widely used in neonatal ICU for its ease of application and interpritation for brain monitoring in hypoxic ischemic encephalopathy. Intensive care physician, nurses, or critical care technologists can apply the electrodes and interpret the aEEG recording independently, without input from a neurologist.

Placement of electrodes :

1. Electrodes were placed on the scalp corresponding to the positions C3, P3, C4, and P4 of the international 10–20 system.
2. A reference electrode was placed on the patients' back or forehead

What are the patterns of aEEG ?

(A) Normal or Continuous Normal Voltage (CNV): upper margin >10 µV and a lower margin >5 µV.

(B) Moderately abnormal or Discontinuous Normal Voltage (DNV): upper margin >10 µV, lower margin <5 µV. The tracing is discontinuous and there is no sleep-wake cycling.

(C) Burst Suppression (BS) is a pattern of mixed inactivity with bursts of higher amplitude.

(D) Suppressed activity or Flat Tracing (FT) is defined by a low voltage/inactive aEEG with amplitude <5 µV; may be called called Continuous Low Voltage (CLV) when the background is around 5 µV.

Weaning continuous infusions:

- 48 hours duration – Wean over 6-12 hours, decrease rate by 15-30% every 2 hours
- >48 hours duration – Slow wean, decrease rate by 15-30% every 6-12 hours
- Consider adding scheduled benzodiazepines or barbiturates for withdrawal for infusions
- >5 days – Add maintenance anti-seizure medications:
- Use doses at high end of therapeutic range
- Consider combinations with multiple different mechanisms

Summary of treatment recommendations

1. The treatment of convulsive SE should occur rapidly and continue sequentially until clinical seizures are halted.
2. Simultaneous assessment, reassessment and critical care management of associated life threating events should continue.
3. Early Emergent therapy – Start with benzodiazepines.

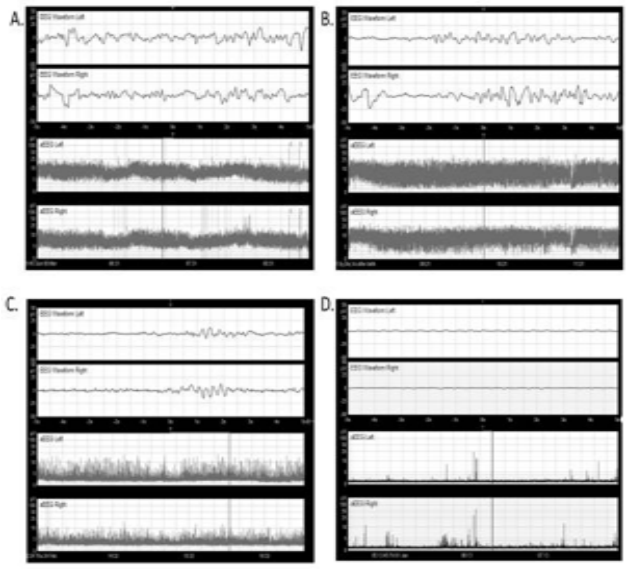

Fig 4. Patterns of tracing in aEEG. (A) Normal or Continuous Normal Voltage (CNV). (B) Moderately abnormal or Discontinuous Normal Voltage (DNV). (C) Burst Suppression (BS) (D) Suppressed activity or Flat Tracing (FT)

a. IV Lorazepam is the preferred choice.
b. Alternatives – IM Midazolam, buccal or intranasal midazolam or rectal diazepam if IV access is not available

4. Urgent control AED therapy recommendations include use of IV fosphenytoin/phenytoin, valproate sodium, or levetiracetam.
5. Continuous infusion AEDs are recommended in Refractory SE therapy. But vary by the patient's underlying condition.
6. Continuous EEG monitoring should be initiated within 1 h of SE onset if ongoing seizures are suspected
7. The duration of cEEG monitoring should be at least 48 h in comatose patients to evaluate for non-convulsive seizures
8. Slow withdrawal of continuous infusion AEDs for RSE should be tried after a period of 24–48 h of electrographic control.

MCQ

1. According to the operational definition seizure lasting longer than what period of time is defined as status epilepticus?

A. 5 minutes
B. 10 minutes
C. 30 minutes
D. 60 minutes

2. Which of the following status epilepticus etiologies would be present more commonly in pediatric patients compared with adult patients?

A. Low antiepileptic drug concentrations
B. Febrile status epilepticus
C. Cerbrovascular accident
D. CNS Tumor

3. Which of the following is the least important short-term treatment goal in managing a hospitalized patient with SE?

A. Identify precipitating factor
B. Stabilize vital signs
C. STAT consult from neurologist.
D. Interrupt clinical or electrographic seizure

4. Which of the following is the drug of first choice in a patient with generalized convulsive status epilepticus?

A. Propofol
B. Lorazepam
C. Pentobarbitol
D. Valproate

5. Which of the following is the drug of choice in preventing seizure recurrence in a patient with generalized convulsive status epilepticus of at least 30 to 60 minutes?

A. Ketamine
B. Phenytoin
C. Propofol
D. Lorazepam

6. Which of the following agents would be the most appropriate agent to use as third-line therapy in a patient with refractory generalized convulsive status epilepticus?

A. Valproate Infusion
B. Midazolam Infusion
C. Lidocaine
D. Paraldehyde

Answer key

1.- A ; 2- B ; 3-C ; 4- B; 5- B; 6-B.

Gifted Children

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Gifted and talented children are those who by virtue of outstanding ability are capable of high performance. They display near-adult level skills and interests. They begin to read fluently at the age of three or four, without any extended instructions. They may play an instrument as skillfully as a highly trained adult. They may show excellent skill in mathematical problem solving from arithmetic to algebra at an age when their peers have just learned to carry numbers in additions. They have quick understandings, insatiable curiosity, extensive information, retentive memory and large vocabulary.

Definition

There is no all-agreed universal definition of gifted children. Giftedness can be defined in several ways. The psychometric definition of giftedness is based on scores obtained in standardized intelligence tests. The two most frequently used cut-off points are 2 standard deviation above the mean (IQ 130-135) and 3 standard deviation above the mean (IQ 145-150). The former score represent upper 2% and later upper 0.1% of IQ distribution[1].

The second definition of giftedness is based on real-life achievement or performance of exceptional skill rather than test scores. Children with special talents (other than general intelligence) in areas such as music, chess, mathematics, drawings, drama fit these descriptions.

Giftedness and talent are often used interchangeably. However, Gange (1985,1991) has differentiated between the two concepts by defining giftedness as above-average competence in human ability and talent as above-average performance in a particular field[2,3]. It means, giftedness refers to human aptitude such as intellectual or creative abilities. Talent is demonstrated in an area of human activity as mathematics, literature or music.

Other definitions of giftedness consider certain personality trait like motivation, commitment, perseverance, high self-esteem and creativity, which allow above average ability to develop exceptional skill. Renzulli (1978, 1986) proposes a three-ring definition in which above average intellectual ability, creativity and task commitment interact to produce giftedness[4].

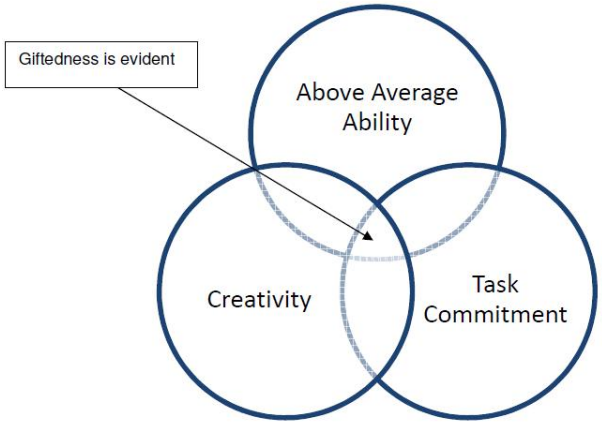

Fig 1. Renzulli's Three-Trait definition

Within above average ability Renzulli makes a difference between general ability (like processing information, integrating experiences and abstract thinking) and specific abilities (like capacity to acquire knowledge, performance in an activity).

By creativity Renzulli means the fluency, flexibility and originality of thought, an openness to experience, sensitivity to stimulations and willingness to take risk.

By task commitment, he indicates motivation turned into action (like perseverance, endurance, hard work) and also self-confidence, perceptiveness and a special fascination with a special subject. Renzulli

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argues that without task commitment high achievement is not possible. Gifted behavior is expressed only if characteristics from all three rings work together[5,6].

Characteristics

Giftedness is not a simple, uniform condition with consistent findings and a predictable course. There is a great diversity among the gifted and talented children. The situation is as complex and fluctuating as the definition of giftedness. According to McAlpine and Reid, 1996, the characteristics of gifted and talented students can be described in the following sections[7].

Motivational characteristics :

Gifted children have a deep intrinsic motivation to master the domain in which they have high ability. They have a powerful interest in their area of giftedness. They are committed and may become absorbed in their tasks (a math book, an instrument, a sketch-pad) so intently that they lose sense of outside world. They are self-directed, set personal goal and prefer to work independently.

Learning characteristics :

Gifted children display logical and analytical thinking. They quickly understand patterns and relationship and easily grasp underlying principles. They like intellectual challenges and jumps stages in learning. They independently want to discover the why and how of things. They have a high grade memory.

Self-determination characteristics :

They have a high self-esteem. They express their ideas, preferences and opinions forthrightly. They question arbitrary decisions and often ask teachers and adults for explanations. They may show interest in adult problems. They usually relate well with older children and often prefer their company. They become easily bored by routine tasks and reluctant to practice skills already mastered.

Creative thinking characteristics :

They produce original ideas. They display imaginations, fantasy and intellectual playfulness. They enjoy speculations and thinking about future. They are not afraid to be different and may seek unusual rather than conventional relationships.

Social leadership characteristics :

They are self-confident and willing to take responsibility. They take initiative in social situations. They actively seek leadership in sporting activities. They can combine ideas from group members to formulate a plan of action.

Vulnerabilities

We should recognize that exceptionality can be a gift and also a burden. While many gifted children exhibit advanced psychosocial adjustment, others may feel isolated and may develop emotional and behavioral problems leading to depression, excessive self-criticism or even eating disorders[8]. Following are some of the vulnerabilities the gifted children may face.

Underachievement :

When intellectually gifted children are not sufficiently challenged, they sometimes lose their motivation and become underachievers. When the parents and school try to force to be well-rounded by curtailing activity in the children's domain of giftedness and forced children to spend time on more normal activities, they may end up destroying the children's drive.

Isolation :

Extreme level of giftedness may lead to isolation. Many gifted children may feel different when they realize that no one of their age thinks like them. Often they think that there is something wrong with them and want desperately to be "like everyone else". In the middle childhood, sometimes profoundly gifted children may try to hide their abilities in the hope of becoming more popular – a desire to fit in with lower performing peers. Gifted children also tend to be introverted and spend more time alone than do others[9].

Perfectionism :

Many gifted children show an inner push towards perfectionism which drives them to set impossible goal for themselves. It should be recognized that some degree of perfectionism is beneficial to achievement, but it can also be debilitating. Perfectionism may become a burden, when it is motivated primarily by a fear of failure or a desire to please others and may be accompanied by excessive self-criticism and an inability to celebrate one's accomplishments[10]. Sometimes the gifted children, because of their sensitivity, may become

excessively concerned about their parent's desire and constantly try to meet their parent's standards rather than their own.

Intensity and sensitivity :

Gifted children express a high level of emotional sensitivity and intensity. They experience their emotion very strongly and react to many situations that may go unnoticed by others or produce only mild reaction. In addition, they may be very sensitive to the feeling of others as well as to criticism and injustice. Although these characteristics can enhance creativity helping individuals to see matters in unusual and original way, they can also be a source of distress if the children are not taught how to cope with them.

Asynchronous development :

Academically gifted children are generally gifted in all academic subjects. They demonstrate giftedness in reading, mathematics and logical analytical thinking. But there are many academically gifted children who present a much less balanced picture. Unevenness between verbal and mathematical abilities is not uncommon. Children gifted in visual arts and in athletics typically show a lack of interest in academic achievement. It has also been seen that children gifted in visual arts are less committed academically than those in athletics[9]. Asynchronous development can be exacerbated if all the energy and time is devoted to the development of the area of giftedness and other aspects of growth are neglected. Special activities and lesson may leave little time for other interests or the development of social skill. As they grow older, adolescents and adult may experience emotional stress and turmoil and the feeling of out of balance.

Self-definition :

The classic adolescent identity crisis may come earlier in highly gifted children. Their intense analytical approach to life leads to early analysis of self. Their perfectionism coupled with inappropriate adult experience can make the process of identity formation difficult. Highly talented children often have potential to succeed in a number of different fields. They may face dilemma deciding which area should engage their minds and talent. Being confused about the direction of their true talent and being worried about the ways they are different from average student, the gifted children may end up with mediocrity.

Identification

Early identification of gifted children is very important. Without early identification and intervention, intellectually gifted children may become disillusioned with school, loose interest in learning. They fail to develop skills because they are never challenged to think and work hard. Gradually they develop a pattern of underachievement and giftedness may end eventually.

Infancy and early childhood is not a good time to determine whether a child is gifted. Early motor milestones generally are not correlated with giftedness[10]. Some early learning (rote learning) such as counting or showing body parts is not correlated with giftedness. Performance on standardized test like Bayley Scale of Infant Development during first 2 years of life is unreliable predictor of intellectual giftedness. Whereas competent reading before school entrance generally (but not always) indicate above average mental ability[11]. But high score in Bayley Scale combined with parent's report can be an effective predictor. The identification of giftedness in older children may involve several factors[12]. Oakland (2005) summarized the process of identification in the following way (Fig.2).

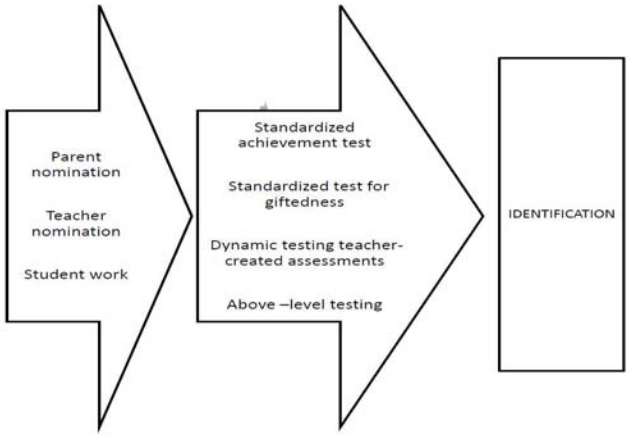

Fig 2. Modified from Oakland T, 2005. 21st century model for identifying for gifted and talented programs in light of conditions: an emphasis on race and ethnicity, Gifted Child Today vol. 28, no.4 pp 56-58.

Difficulties in identification

Identification of giftedness becomes difficult in some situations. Giftedness is harder to identify in physically handicapped children. Their physical needs are major concern rather than their academic or artistic potential. Moreover, poor self-esteem associated with the disability may prevent these children from realizing their potential. Giftedness is also difficult to be identified in children who have learning disabilities. They are exceptional in two ways (so called 2-e children). It has been estimated that about 10% of gifted children have a reading problem. Albert Einstein, Auguste Rodin and John D Rockefeller are famous example of brilliant individual who had reading and writing problems. Affected children have amazing abilities in one area (music, drawing, mathematics, memory) but delayed in other aspects. Moreover, some of them may have behavioral problems like repetitive behavior, little use of language and social withdrawal resembling autism[1]. Giftedness also likely to be unnoticed in children from low socioeconomic status. Gifted children from minority culture are also less likely to be identified.

Management

Supporting and nurturing a gifted child is critical and tremendously rewarding. A pediatrician can support, guide and advocate for these children and their families. Families play a central role in developing the talent of gifted children.

The role of family

Like all children, gifted children also need a loving, responsive and stimulating parenting. Parents of gifted children may feel inadequate fearing that the child is smarter than them. The pediatrician can help the parent and other family members to maintain their self-esteem. Sometimes the parents may be overwhelmed with complex questions from their pre-school children like origin of life, creation of universe, religion or God, poverty, homelessness or world hunger. In this situation the parent should admit that they do not know all the answers but try together with their child to find the answers. The parents should be encouraged to treat the gifted children in the same way as they do their other children. Otherwise, the siblings will feel inferior or neglected. The siblings may feel inferior particularly if the gifted children surpass them in school. Tension may be magnified if gifted children become friend of their older sibling's friend. To preserve the sense of self-worth and competence in siblings, the pediatrician should recommend to the parents that they should spend special time with each of their children. Parents also should encourage other talents in siblings.

Pediatrician should also warn parents about putting too much pressure on their gifted children. They should allow the children to have free time for unstructured play. Play affords many opportunities for self learning, interaction with peers and development of creativity and initiative. Gifted children may prefer to play with older children whose interest and abilities are closer to their own. But this should be allowed as long as these relationships are healthy. If children have a rich environment with plenty of objects and books to explore, diverse experiences and stimulating interaction they will develop their own interest.

Sometimes the families of the gifted children may be stressed by the extra demand on their time, energy and money. Such conditions may damage family relationship if they are not recognized and overcome. The pediatrician can help parents to balance between nurturing talent and normal development.

At school

One of the common questions that the parents of gifted children ask the pediatrician is related to educational decision. There are two educational options – acceleration and enrichment. The parents of the school aged children have to decide whether acceleration or enrichment is more appropriate. The choice depends on the particular child.

Acceleration :

Acceleration means starting school earlier or skipping grades. Parents and teachers are usually concerned that children in acceleration program may have problems with social adjustment if their classmates are older. However, existing evidences suggest that the gifted children benefit socially from acceleration. Gifted children also make up any curricular content missed by grade skipping. But the

decision and process of acceleration is difficult to reverse. So it may not be the best option when the decision is the borderline one.

Enrichment :

It involves keeping children with same-age classmates, but supplementing the regular curriculum. The teacher and school should be willing to offer extra work (e.g. special project) in addition to grade level assignment. This program may work well with some gifted children. But it depends on resource, funding available and in large part on the experience and enthusiasm of the teachers involved. Some enrichment program may isolate gifted from non-gifted children and labeling the gifted children as elite. Sometimes, a combination of acceleration and enrichment programs is the best option. Acceleration may not be sufficient for markedly advanced students, because they would have to skip 2 to 3 grades to be appropriately challenged. Whereas, acceleration may be a better option for a large outgoing child than for a small one. But acceleration should be discouraged if a child's social and behavioral development lags significantly behind his intellectual development[8]. It is also important to ask the gifted children what they would like to do.

The prognosis of gifted children is excellent. Pediatrician can serve as a resource for parents in raising their gifted child and help the child and family to obtain appropriate evaluation, educational programs and supportive resources.

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COVID-19 Encephalitis with Acute Encephalopathy, Biphasic Seizures and Late Diffusion Restriction (AESD)

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Abstract : *1 year 3 month old girl presented with seizures with biphasic course. She was COVID 19 positive and was mechanically ventilated for protection of airways in view refractory seizures. Magnetic resonance imaging (MRI) brain MRI Brain showed diffusion restriction with low apparent diffusion coefficient (ADC) values involving bilateral frontal, parietal, occipital and temporal subcortical white matter, more on the left. Her clinical course and diffusion abnormalities on MRI were consistent with those of acute encephalopathy with biphasic seizures and late diffusion restriction (AESD).*

Keywords *: COVID Encephalitis, AESD, encephalopathy, seizure.*

Introduction

While patients with COVID-19 typically present with fever, shortness of breath, and cough, neurologic manifestations have been reported, although to a much lesser extent[1]. Herein, we report a case of COVID-19–associated acute encephalopathy with biphasic seizure and late diffusion restriction, a rare encephalopathy that has been associated with other viral infections but has yet to be demonstrated as a result of COVID-19 infection.

Case report

1year 3 months, previously well 1st twin, born of non consanguinous parents by LUCS at term with birth weight of 1.8 kg, presented with high fever for 3 days and prolonged convulsions. She was admitted locally, treated with Phenytoin and Phenobarbitone and was transferred to higher centre in view of low GCS, continued seizures and deranged liver function. CSF showed pleocytosis (200 cells) with raised protein (88.3 mg/dl) and reduced glucose (65 mg/dl). Gram stain and culture were negative. CT brain was normal.

On presentation, she was having convulsions, which was controlled with intravenous Lorazepam. GCS was E2V4M4. She was febrile with warm peripheries. Liver was soft and palpable below the right costal margin, no splenomegaly or ascites. 3% saline infusion and Levetiracetam were started. Invasive blood pressure (BP) was low with wide pulse pressure. ABG showed metabolic acidosis with respiratory compensation, mostly hyperchloremic. Normal saline bolus was also given. Noradrenaline and adrenaline infusion were started. She continued to have frequent seizures without gaining consciousness in between. She was intubated and ventilated for protection of airway and started on Midazolam infusion.

COVID-19 CBNAAT was positive. Serum ammonia was normal (17 mcg/dl), INR raised (1.32), Triglyceride was high (213 mg/dl), Fibrinogen normal (325 mg/dl), transaminase raised (AST 1560 U/L, ALT 2734 U/L, total protein (4.7 g/dl) and albumin (2.7 g/dl) were low. Inflammatory markers were raised, CRP 32.7 mg/L, Procalcitonin 20.99 ng/ml, IL 6 31.1 pg/ml and D dimer 5.34 mcg/ml. Scrub typhus, Dengue NS1 and malaria tests were negative. USG abdomen was normal.

N-acetyl cysteine was started 100 mg/kg/day. Immunoglobulin infusion 2g/kg was given. Dexamethasone injection was also given. Midazolam and Fentanyl infusion were continued. Remdesivir was not started since ALT was more than 5 times normal.

Ventilator requirements remained modest with good gaseous exchange. Hemodynamic status remained

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unstable with low BP and very wide pulse pressure. Vasopressin infusion was started. Echo-cardiography showed structurally normal heart except a small PFO with left to right shunt, normal LV function, LVEF 70% and normal coronary arteries.

On examination Doll's eye movement was present, pupils were 6 mm, equal and reacting to light and asymmetry of movement with relative paucity on the right side was noted. Planter was flexor bilaterally. EEG showed features of encephalopathy. IV Methyl prednisolone 30 mg/kg/day was given for 5 days followed by oral prednisolone 1mg/kg daily, gradually tapered and stopped over 1 month. She became afebrile but continued to have seizures for which dose of Levetiracetam was increased and IV Lacosamide was added. MRI Brain showed diffusion restriction with low ADC values involving bilateral frontal, parietal, occipital and temporal subcortical white matter, more on the left, suggestive of AESD, shown in Figure 1. Intermittent seizures continued and Topiramate was added, loading followed by maintenance. L-carnitine, folic acid and vitamin B12 were given. Dose of Levetiracetam and Topiramate was increased and Clobazam was added. Persistent abnormal choreoathetoid movements involving the right side of the body was noted for which oral Tetrabenzine was added.

Episodes of unexplained hypotension and hypertension were noted and autonomic dysfunction was suspected. Repeat echo-cardiography was normal except the PFO. She remained convulsion free for 6 days following which she developed seizures again for which dose of Topiramate was further increased. Increased muscle tone was noted (right>left), deep tendon reflexes were exaggerated and bilateral planters were extensor.

Repeat COVID-19 test after 14 days was still positive. Repeat blood tests for inflammatory markers were normal. Patient was extubated after 16 days and developed stridor which was managed with Adrenaline and Budesonide nebulization for 3 days. COVID 19 after 21 days became negative.

Minimal drooling and oropharyngeal pooling of secretions was noted which gradually improved. Swallow was initially unsafe and nasogastric tube feeding was continued. Repeat swallow assessment done every 5 days showed gradual improvement and oral feeding with pureed diet was established 14 days post extubation. Anticonvulsants were gradually made oral. Bluish discolouration of left great toe was noted. Doppler study of both lower limbs was normal. D dimer (11.75 mcg/ml) and Fibrinogen (498 mg/dl) were raised and PT, APTT, INR was normal. Subcutaneous Enoxaparin was started. Repeat D dimer was normal and Enoxaparin was stopped.

Regular physiotherapy was continued and mother was trained to feed and take proper care of the baby

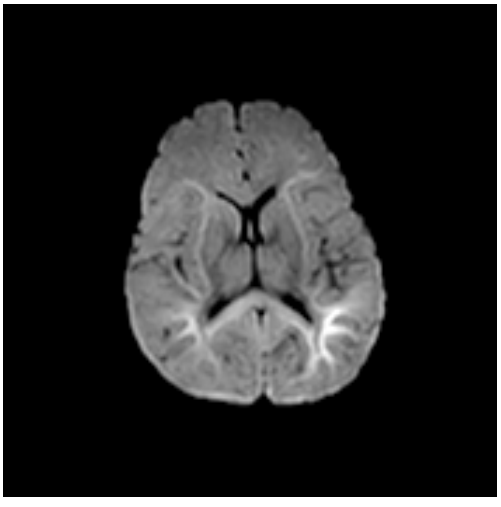

Fig1: MRI Brain showing diffusion restriction with low ADC values involving bilateral frontal, parietal, occipital and temporal subcortical white matter, more on the left, suggestive of AESD.

and she was discharged on oral medications and advice to follow up.

Discussion

AESD is a syndrome of encephalopathy characterized by prolonged febrile seizure followed by a cluster of subsequent seizures several days later (biphasic seizures) and altered consciousness in the acute stage followed in the sub-acute stage by restricted diffusion in the subcortical white matter on magnetic resonance imaging[2,3].

The Aetiology of AESD has been attributed to viral infection like influenza A and human herpes virus 6 or a bacterial infection, *Streptococcus pneumoniae*[4,5,6]. The exact pathogenesis of AESD is uncertain.

Reduced diffusion in the bilateral hemispheres can be seen with other causes, such as hypoxic-

ischemic encephalopathy and shaken infant syndrome. Encephalopathy due to substance abuse or intoxication may exhibit similar diffusion abnormalities. In our patient, there was no evidence of hypoxia-ischemia, non-accidental head injury, or substance intoxication.

Okumura, *et al*, described two distinct patterns of brain lesions on the diffusion-weighted image (DWI) in cases of AESD, diffuse lesions and central-sparing lesions[3]. Diffuse lesions are defined as reduced diffusion in the whole cortex and/or subcortical white matter in the bilateral hemisphere during the clinical course, mainly during the subacute stage. In some patients, reduced diffusion in the frontal and occipital areas may precede diffuse lesions. Central-sparing lesions are characterized by lack of reduced diffusion in areas around the bilateral Sylvian fissures and perirolandic region. In both types of AESD, no restricted diffusion is seen in the basal ganglia and thalami throughout the clinical course. Patients with central-sparing lesions appear to represent a relatively mild phenotype of acute encephalopathy. Coma is uncommon and laboratory abnormalities in the form of elevated liver enzymes are mild if present. Death is uncommon in central sparing lesions, though various degrees of cognitive impairment are observed as neurologic sequelae. Onset is often marked by a prolonged seizure followed by improved consciousness. However, clustered seizures, signs of frontal lobe dysfunction, and worsening of consciousness become apparent at 3–4 days after onset. It is postulated that pathogenesis of acute encephalopathy with central-sparing lesions may be different from that of acute encephalopathy with diffuse lesions. Some authors have suggested that this subtype of acute encephalopathy is caused by excitotoxicity[7,8] because prolonged seizures are often observed at the onset of AESD.

Key message

Given that there is limited data on neurological symptoms, health care providers benefit from accurate and real-life data to better treat their patients. If patients with neurological conditions are not considered to have COVID-19, this may present a nationwide issue to health care team members treating patients and in turn the general public if they are discharged and further exposed to other people.

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Saga of Short Stature: Two Unusual Cases

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Common causes of short stature

- Undernutrition
- Chronic systemic disease
- Cerebral palsy
- Malabsorption
- Growth hormone deficiency, Cushing syndrome
- Skeletal dysplasia – Spondylometaphyseal, spondyloepiphyseal dysplasia
- Genetic syndromes – Turner syndrome, Down syndrome.

Physiological short stature is height between -2 to -3 standard deviations.

Causes of physiological short stature

- Familial
- Constitutional

Case 1

Seckel syndrome or micro cephalic primordial dwarfism (also known as bird headed dwarfism, Harper's syndrome, Virchow-Seckel dwarfism, and Bird-headed dwarf of Seckel)[1] is an extremely rare congenital autosomicdisorder. The syndrome is named after an American physician, Helmut Paul George Seckel[2]. Harper's syndrome, a term often used as a synonym for the Seckel syndrome, was named after Rita G. Harper[3]. Characterised by severe intrauterine and postnatal growth retardation, microcephaly, proportionate dwarfism, and typical bird-like facial appearance with skeletal and brain abnormalities. It can be due to defect in ATR signalling pathway. Incidence of case reported shows female preponderance. Birth weight is usually low, mean birth weight ranging from 1 kg to 2.5 kg, also noticed in our case. Head circumference decrease in almost all cases and 50% cases shows association with decreased height.

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Case scenario

A 16-year-old girl presented in the Department of Paediatrics of IQ CITY Medical College and Hospital, Durgapur, WB with fever and increased frequency of micturition. The girl was born at home with low birth weight (mother could not tell actual birth weight). Parents noticed delay in the growth of the child in comparison to other child of same age. On general examination head circumference was about 41cm (microcephaly), height was 83 cm(Fig 1), nasal bridge depressed and nose was almost as the shape of bird's beak, low set ears, dental hypoplasia (hypodontia) (Fig: 2). On systemic examination no abnormalities noted. On limited skeletal survey there is (Fig 3) presence of scoliosis, thoracic dystrophy and 11 pair of ribs in chest X- ray PA view and [Fig 4] X-ray pelvis AP view showing flaring of the ileal bones and short pelvis. As the parents came to know that there is no permanent cure and as the patient was girl child, no further investigations and no further visit to the doctor's clinic was done by them.

Discussion :

Seckel Syndrome is a rare, congenital heterogenous autosomal recessive disorder with an incidence of 1:10,000 in live born children[4,5] presenting at birth. Characterised by growth delays prior to birth{IUGR} resulting in LBW and delay in growth continue after birth{postnatal} , resulting in short stature with proportional development of upper and lower limbs. The pathophysiology of this syndrome can be attributed to the defects in the ATR (ataxia telangiectasia and rad-3 protein) signalling pathway.

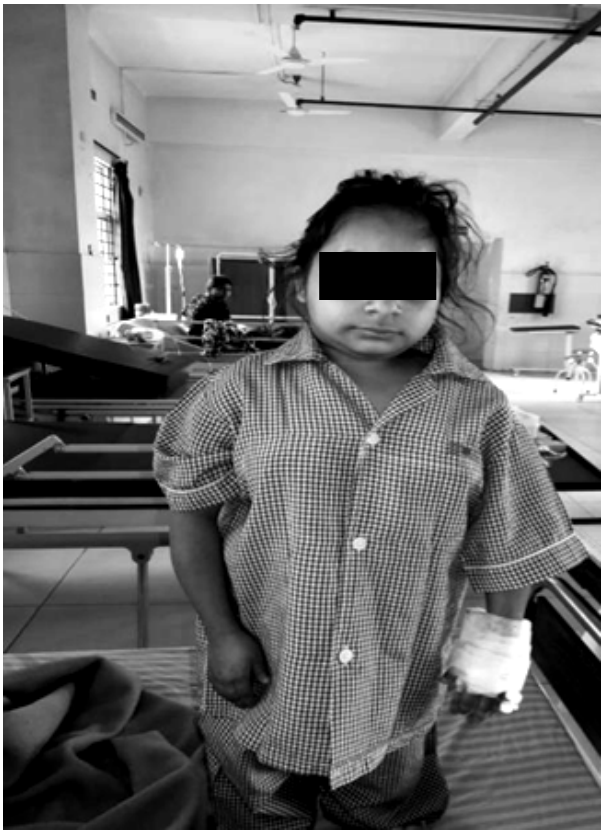

Fig 1:Short stature

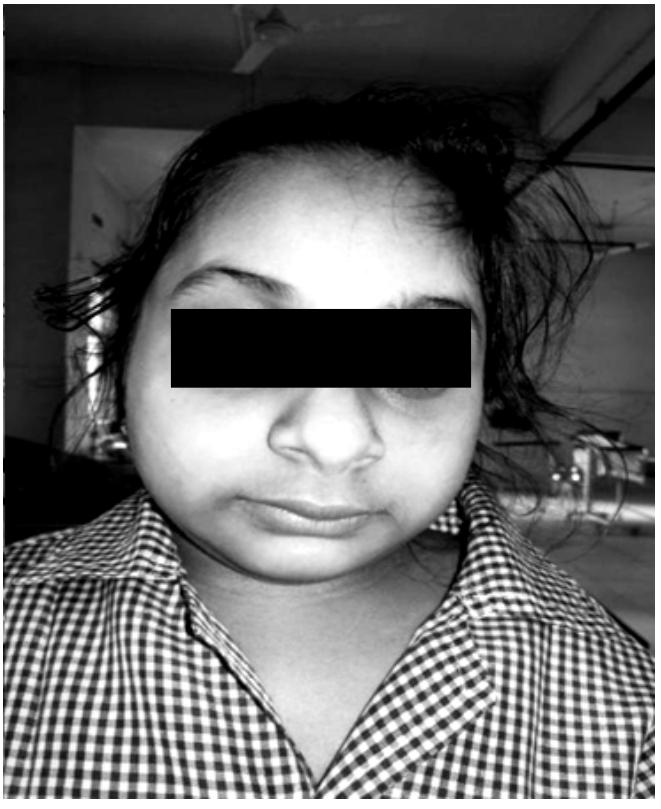

Fig 2: Typical facies: Bird's beak nose

Radiological examinations:

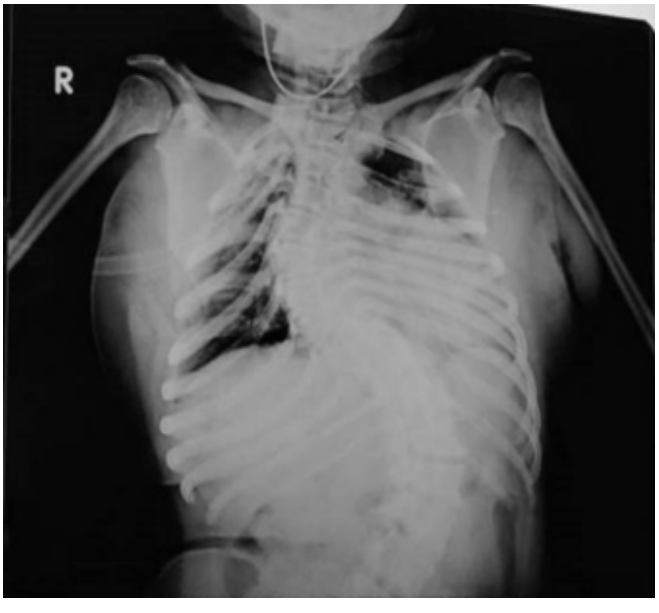

Fig 3 :Chest X-ray PA view showing 11 pairs of ribs, thoracic dystrophy, scoliosis

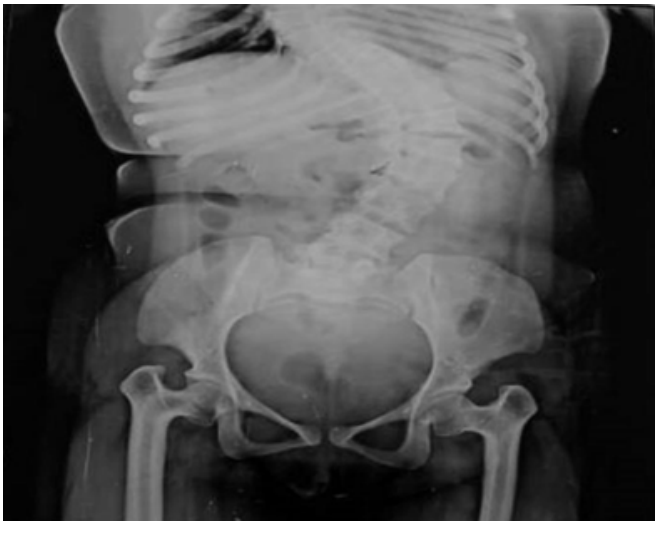

Fig 4 :Xray pelvis AP view showing flaring of ileal bones with short pelvis

An important function of ATR is the coordination of responses to replication fork stalling, which arises during normal replication possibly as a consequence of endogenous DNA damage. These are characterized as ATR-Seckel cells. Seckel syndrome is clinically and genetically heterogeneous with defective gene localized to 3q21-24 causing mutational changes[6]. Also known as bird headed dwarfism, microcephalic primordial dwarfism , nanocephalic dwarfism. Major abnormalities are – microcephaly, micrognathia, beak like nose. In some cases craniosynostosis, strabismus, low set and malformed ears with absent earlobes, cleftpalate, dental hypoplasia, radial dislocation, inability to fully extend the knees. In some cases, pancytopenia, cryptorchidism, clitoromegaly, simian crease, hirsutism.

Differential diagnosis of this syndrome are Dubowitz syndrome, fetal alcohol syndrome, trisomy 18, bloom syndrome. Most of these syndrome show features such as microcephaly, facial asymmetry, micrognathia and discrepancy of mid facial region. However, Seckel syndrome depicts other features such as delayed cranial sutures , large lobe-less ears , apertognathia, large nose and relatively small mandible, which are mostly seen in our case[7,8].

Management

Is directed towards prevention of associated complications like atrial septal defect, cardiac arrhythmias and other renal disorders[9,10].

The present case was seen by paediatrician to assess the general health status of patient, UTI treatment, then followed by psychiatric advice to comment on mental status of patient, intelligence quotient was about normal so the patient was kept for follow up as at present patient was not ready for cosmetic surgical intervention.

Conclusion

Seckel syndrome is a rare autosomal recessive disorder caused due to mutation of gene leading to chromosome instability causing various skeletal, physical, mental and hormonal changes. In this case there is proportionate delay in growth, vertebral anomaly, beak shaped nose, delayed dentition. So by exclusion we came to the diagnosis of Seckel syndrome. Genetic studies could not to be done. So on the basis of clinical and some radiological findings most probably the case is of Seckel syndrome.

Declaration of patient consent:

I certify that I have obtained all appropriate consent from the patient. The patient understand that her name and initials will not be published and due efforts will be made to conceal the identity but anonymity cannot be guaranteed.

Case 2

Hyperparathyroidism is defined as overproduction of parathyroid hormones. Primary hyperparathyroidism is excess secretion of parathyroid hormones from one or more parathyroid glands and is associated with familial Multiple Endocrine Neoplasia (MEN) syndrome[11]. Mostly it is due to single adenoma[12]. Secondary hyper-parathyroidism occurs when secretion of parathyroid hormones increases to compensate for prolonged hypocalcemia. It occurs mostly due to renal failure. In severe vitamin D deficiency- limb deformities and pathological fracture seen[13]. It is very rare in paediatric population.

Case scenario

A 14-year-old female child presented in the Department of Pediatrics of M.G.M. Medical College and Lions Seva Kendra Hospital, Kishanganj with the complaint of delayed developmental milestone and severe growth retardation. She was born at 36 weeks by C-section (breech presentation, polyhydramnios) at hospital with birth weight of 1.5 kg. She had an abnormal short stature with a weight of 12 kg, height 90cm and head circumference 46cm. General examination revealed microcephaly, receding, sloped forehead and chin, beaked-like protrusion of nose, ataxic gait. On systemic examination no abnormalities noted.

On ultrasound examination of whole abdomen poor cortico-medullary differentiation of bilateral kidney with nephrolithiasis and nephrocalcinosis was seen. On limited skeletal survey there was osteopenia and tibiofibular synostosis[14](Fig 5). X-ray lower limb lateral view, left tibia shows anterior bowing with pseudoarthrosis. Hormone estimation revealed high parathyroid hormone level[15] with normal serum calcium and serum phosphate. Serum creatinine was 1.32mg/dl, increased GFR. Magnetic resonance imaging shows no any obvious changes.

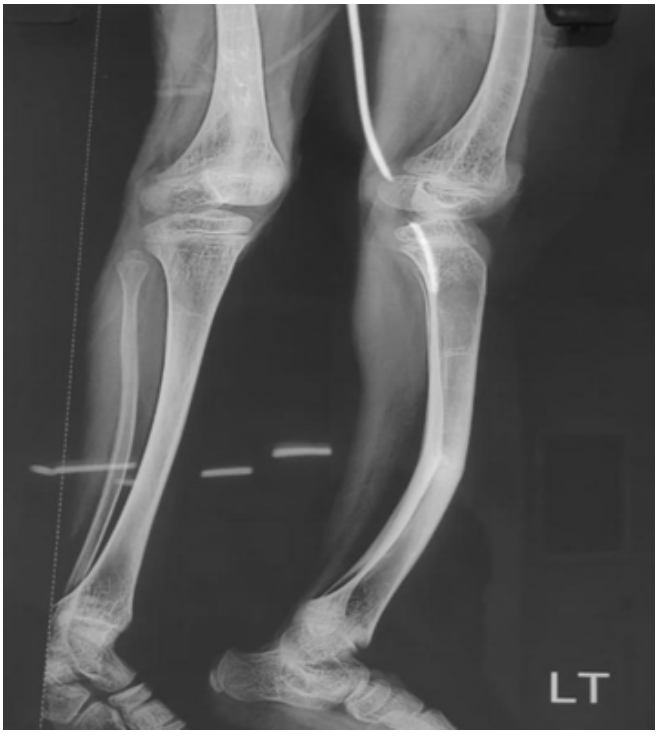

Fig 5: X-ray lower limb lateral view

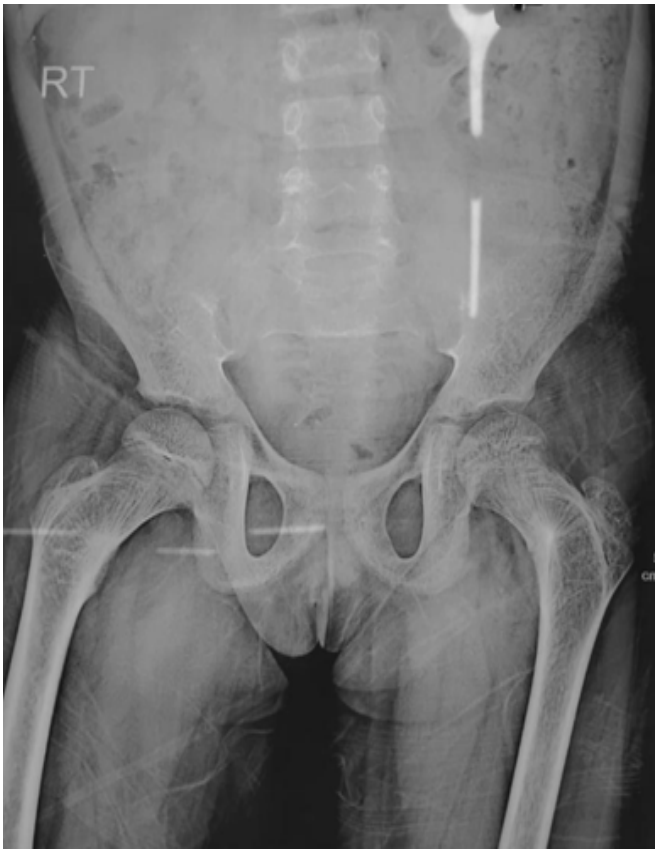

Fig 6 : X-ray pelvis AP View

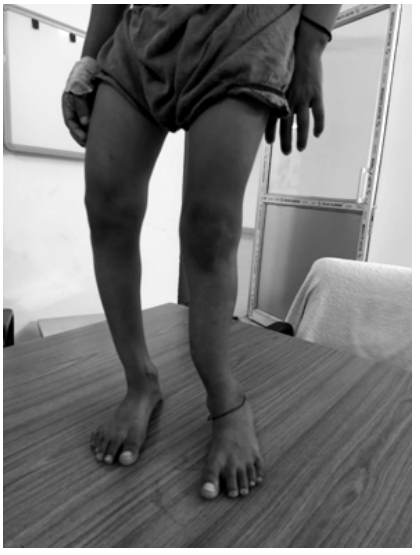

Fig 7: Anterior bowing of left leg

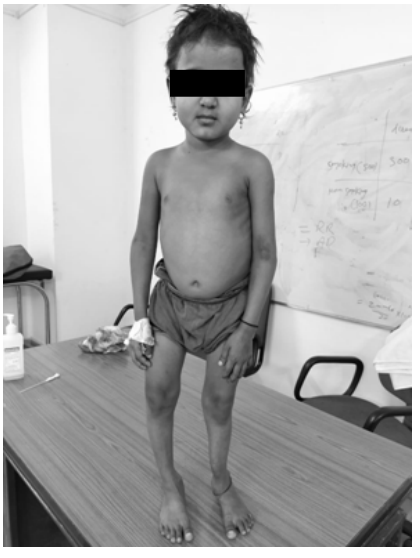

Fig 8: Short stature with bow legs

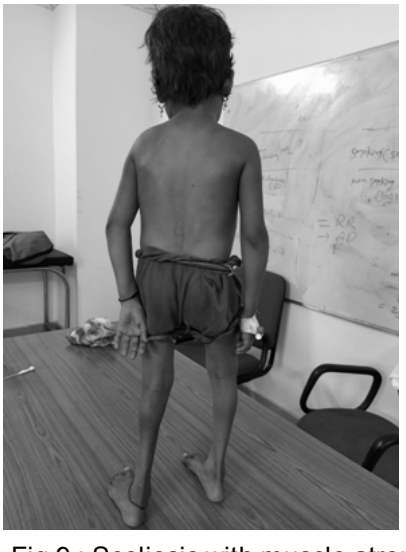

Fig 9 : Scoliosis with muscle atrophy

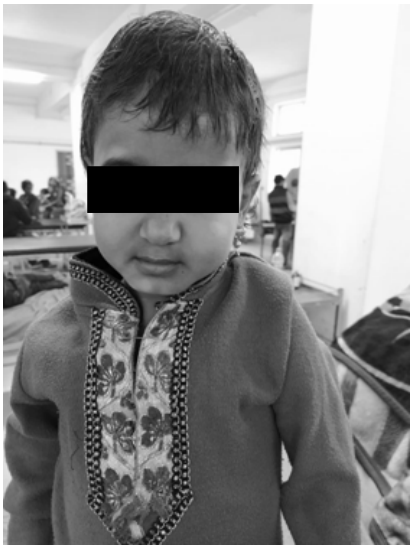

Fig10 : Showing sparse hair

Discussion

We are presenting a case of Short stature associated with secondary hyperparathyroidism. In our case clinical findings are muscular atrophy , bowing of long bones[16] ; on lab investigations level of parathyroid hormone elevated with normal calcium and phosphate level; on ultrasound imaging there is bilateral poor corticomedullary differentiation with nephrolithiasis and nephrocalcinosis.

Confirmation of diagnosis

Proper clinical examination, laboratory findings and radiological imaging techniques for bony deformities required for confirmation of diagnosis.

Declaration of patient consent :

I certify that I have obtained all appropriate consent from the patient. The patient understand that her name and initials will not be published and due efforts will be made to conceal the identity but anonymity cannot be guaranteed.

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Hepatic Decompensation In Delayed Presenting Biliary Atresia – A Salvage

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Background: *Patient with biliary atresia may present late at a time when diversion operation may not be possible. Liver transplantation is the last resort in these cases with hepatic decompensation.*

Case characteristics: *4 month old baby presenting with jaundice and ascites.*

Observations: *Maternal donor liver and post transplant combination therapy with Prednisolone, Tacrolimus and Mycophenolate resulted in minimal complications and no symptoms of graft rejection.*

Message: *Early diagnosis of Biliary atresia is important. But late presentation with hepatic decompensation can be treated with liver transplantation with appropriate post-transplant care.*

Biliary atresia is characterised by obliteration or discontinuity of intrahepatic and/or extrahepatic biliary system resulting in obstruction of bile flow. Incidence is about 1 in 10000 to 15000 live births. It can be classified as Cystic and Non-cystic. Commonest being Non-cystic third type with non-patency of entire extrahepatic biliary system and intrahepatic ducts at hilum. Hepatoportoenterostomy (Kasai) operation should be done as early as possible. Liver transplantation is the ultimate resort.

Case report

A 4 month old female infant presented with history of clay-coloured stool since birth, progressively deepening jaundice and abdominal distension since last 2 months.There was no history of fever, lethargy, poor feeding, decreased urine output. The baby was born at term by LSCS. Birth weight 2.7 kg. No history of GDM, PIH, hypothyroidism or other antenatal complications in the mother. No maternal history of fever with rash antenataly. There was no history of neonatal complications.The baby cried after birth. No history of neonatal jaundice. She was the first - born child, of no-consanguinous marriage.

On admission, there was marked icterus. Hepatomegaly 8 cm below the right costal margin along miclavicular line. Splenomegaly 5 cm below left costal margin along splenic axis. No developmental delay. Anthropometric measurements were within normal limits.

On investigation, the serum total bilirubin was markedly raised (13.2 mg/dl) with direct bilirubin of 8.7 mg/dl. Liver enzymes were raised(SGOT-338, SGPT-112). The elevation of ALP(738 IU/L) and GGT(1319 IU/L) suggested obstructive etiology.

USG W/A was suggestive of biliary atresia. So a liver biopsy was done which showed marked portal fibrosis.

The baby was started on vitamin A,D,E,K supplementation, Ursodeoxycholic acid and multivitamin drops and planned for liver transplantation.

In the meantime, the baby developed progressive abdominal distension, pedal edema, marked pallor, increasing icterus , poor feeding.

CT scan abdomen done showed signs of portal hypertension. This was not present initially and was a new development.

Blood transfusion and albumin infusion were given. Repeated ascitic fluid tapping was done. Baby put on antibiotics in view of repeated fever spikes.

Condition of the baby stabilised and liver transplantation done, mother was the donor.

The baby recovered well following transplantation

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except development of mild hypertension which was managed with Nifedipine and subsequently Propanolol.

The baby was discharged with immunosuppresants Prednisolone,Tacrolimus and Mycophenolate along with Ecosprin and Nifedipine.

Follow-up at 1 and 2 months following transplantation showed progressive decline in liver enzymes. The Total bilirubin at 2 months following transplant was 0.59 mg/dl.

USG abdomen done 3 months post-transplant showed normal hepatic artery and portal venous flow. No intrahepatic biliary duct dilatation.No evidence of ascites.

The baby is kept at regular follow-up with CBC, Serum Tacrolimus level,Creatinine and LFT every 2 weekly, CMV PCR every 3 monthly, and Lipid profile and Thyroid profile every 6 monthly.

USG Abdomen for Intrahepatic duct and Doppler monthly for 3 months and then 3 monthly were advised on follow-up.

Discussion

Most patients(85-90%) with biliary atresia are normal at birth. Usually postnatal progressive obliteration of bile ducts occur. The embryonic or fetal onset form manifests at birth and may be associated with other congenital anomalies (situs inversus, polysplenia, intestinal malrotation, complex congenital heart disease).

Screening for biliary atresia is indicated in high-risk areas with stool colour cards. Also any newborn with new-onset or persistent jaundice beyond 8 weeks of age should be screened with total and direct bilirubin to detect cholestasis.

It is important to differentiate Biliary atresia from Neonatal hepatitis from history, clinical, biochemical and radiological features.

Hepatoportoenterostomy should be performed as early as possible. Best results if performed less than 8 weeks age. Ultimately most require liver transplantation.

Left lateral segment of donor liver is used in small pediatric recipients. Live donor graft showed less rejection than deceased donor graft in <3 year old.

Post-transplant corticosteroid act through suppression of antibody production and cytokine synthesis, decreasing proliferation of T cells, B cells and neutrophils. Maintainance immunosuppression is achieved by calcineurin inhibitors. They inhibit T-cell mediated acute cellular rejection. Mycophenolate helps to decrease the dose of calcineurin inhibitors and also to manage chronic rejection.

Hepatic artery thrombosis, Portal vein thrombosis, Primary graft non-function are some of the complications of liver transplantation. Rejection usually occurs within the first 90 days. Most common transplant related infections are CMV and EBV.

Our patient presented late with hepatic decompensation, so we proceeded with liver transplantation. Donor was mother which may have contributed to minimal complication following the transplant. No features suggestive of rejection at 3 months post-transplant. No evidence of arterial / venous thrombosis or biliary strictures in follow-up USG. Strict monitoring of serum Tacrolimus level is important both to prevent rejection and avoid complications. Prednisolone and Mycophenolate together with Tacrolimus may be an effective combination in preventing rejection.

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Neonate with Multiple Subcutaneous Lumpy Swellings

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Introduction

Although Subcutaneous Fat Necrosis (SCFN) is a self-limiting condition, recognition of this entity is important, as affected infants require monitoring for associated hypercalcemia or other complications.It is also important to differentiate it from other more sinister conditions like sepsis induced sclerema to avoid unnecessary use of antibiotics. SCFN generally has a good outcome, with spontaneous resolution over weeks to months.

Case report

A one month 10 days old female baby presented with multiple lumpy swelling under the skin all over the body including the front and back of trunk and all the limbs. Those were first noticed by the parents a few days after birth and were gradually increasing in size and number. The swellings were of skin colour, firm, non-tender, free from the underlying structures and also free from the skin. The overlying skin was normal. The baby was otherwise active and feeding well.

She was born by caesarean section at term through meconium stained liquor. She did not cry at birth and had to be admitted to neonatal intensive care unit for 5 days and was roomed-in with mother on day 5. The mother-baby duo were discharged on day 8 in a satisfactory condition. Parents noticed the swellings a few days after discharge.

On examination, the baby was active and sucking well. There was no abnormality of tone and reflexes. There was no other systemic abnormality.

On investigations, her hemoglobin level was 12.6 gm /dl, total leucocyte count 15,700 /mm^3, platelet count 3.9 lac/mm^3. C-reactive protein level was 0.67mg/dl(N-<0.5mg/dl). Total serum calcium was 10.6 mg/dl and phosphorus level was 6.2mg/dl. Serum triglyceride was 418mg/dl and cholesterol was 110mg/dl. Liver and renal function tests were normal. Blood and urine culture reported no growth.

Ultrasonography of the swollen areas revealed multiple nodular fatty tissue with edema. Underlying muscular tissue appeared to be normal. X-ray did not reveal any bony abnormality.The parents were reassured and the baby was kept under follow up. The baby remained active showing satisfactory growth. The swellings started regressing from 3 months of age , disappearing completely by 6 onths.

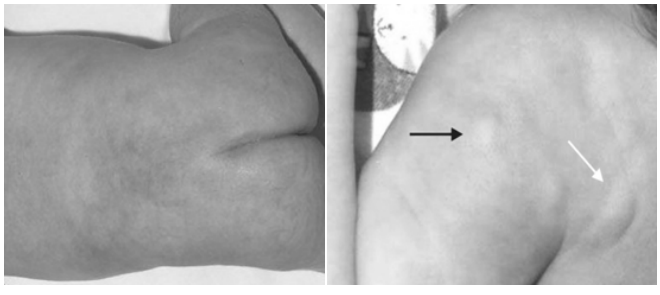

Fig 1. Multiple nodular swellings under the skin

Neonatal risk factors	Maternal risk factors
Umbilical cord prolapse	Preeclampsia
Meconium aspiration	Maternal diabetes mellitus
Perinatal asphyxia	Maternal medications (calcium channel blockers, cocaine)
Therapeutic hypothermia	
Neonatal sepsis	Smoking or exposure to passive smoking during pregnancy
	Materno-fetal Rh incompatibility

Discussion

Subcutaneous fat necrosis (SCFN) is a rare fat tissue inflammation of the newborn. Risk factors include cord prolapse, perinatal asphyxia,

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therapeutic hypothermia, meconium aspiration, and sepsis[1-3].

The pathogenesis of subcutaneous fat necrosis of the newborn (SCFN) is not exactly known. One hypothesis is that SCFN results from the combination of local tissue hypoxia and mechanical pressure; another suggests that the enrichment of stearic acids and saturated palmitic acids in neonatal fat predisposes the tissue to crystallization at low temperatures. As the majority of reported cases of SCFN have developed in the setting of hypoxia or hypothermia, these hypotheses are attractive, although the exact pathogenetic mechanisms are unclear[4,5].

SCFN is usually a benign condition. Nevertheless, it may be associated with thrombocytopenia, hypoglycemia, hypercalcemia, and hypertriglyceridemia.These metabolic derangements may, in turn, represent a possible risk for serious complications.Thrombocytopenia is usually synchronous with the appearance of subcutaneous nodules, and it is possibly caused by peripheral platelet sequestration into the lesions. Hypoglycemia is reported in literature as another risk factor linked to SCFN, but rather than being a cause of SCFN it seems to be itself a consequence of hypoxia. Hypertriglyceridemia is caused by mobilization of fatty acids from adipose tissue. Hypercalcemia is found in 25% of cases and represents the most serious potential complication, associated with significant mortality and morbidity. The first 6 weeks of life represent the time frame at highest risk for clinically significant hypercalcemia in SCFN, with 40% of cases occurring in this lapse of time.Serum calcium starts to rise as SCFN lesions begin to regress; sometimes, hypercalcemia is already detectable before the onset of subcutaneous lesions.Neonates with hypercalcemia tend to present with lethargy, hypotonia, irritability, vomiting, polyuria, polydipsia, constipation, and dehydration . Infants suspected to be having SCFN need to be monitored for these serious complications. If left untreated, moderate to severe hypercalcemia may lead to complications as nephrocalcinosis, nephrolithiasis, renal failure; calcification of falx cerebri, skin, myocardium, and gastric mucosa may also occur[6-8].

Conclusions

Subcutaneous fat necrosis is usually a transient and self-limited condition. However, it may be complicated by thrombocytopenia, hypoglycemia, hypercalcemia, and hypertriglyceridemia. It is pivotal to monitor newborns with SCFN to avoid the risk of serious complications, with particular reference to hypercalcemia. Regular monitoring of serum calcium is recommended until the age of 6 months, in infants with personal history of SCFN.

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Drug Induced Hepatitis in Nephrotic Syndrome with Latent Tuberculosis

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Background: *Both nephrotic syndrome and tuberculosis are common in children in India. Steroids used in nephrotic syndrome can cause flaring of TB. Keeping an eye on ATD induced hepatitis is important.*

Case characteristics: *A 2 ½ year old child with Nephrotic syndrome and antituberculous drug-induced hepatitis.*

Observations: *In asymptomatic child with positive tuberculin sensitivity test, latent Tuberculosis Infection treatment protocol to be followed.*

Message:*Tuberculin skin test is mandatory before starting steroids in nephrotic syndrome. ATD induced hepatitis should be monitored well. Child with TST positive with no symptoms should be treated as per LTBI protocol.*

Nephrotic syndrome is a renal disorder characterised by heavy proteinuria (>40 mg/m^2/hr), hypoalbuminemia (<2.5 gm/dl), edema and hyperlipidemia (cholesterol>200 mg/dl). Minimal change disease is the commonest pathology in children. The incidence in India is 90-100 per million population. Minimal change disease generally responds to corticosteroids. The risk associated with steroid therapy is flaring up of latent tuberculosis infection. Tuberculosis is endemic in India. Tuberculin sensitivity test (TST) should be done routinely before starting steroid therapy.

Case report

A female child, age 2.5 years, was admitted with history of generalised swelling of the body and decreased urine output for last 3 weeks. The first episode of nephrotic syndrome occurred 2 months back. The child was treated inadequately with 3 weeks of daily steroids at a local facility and then put on alternate day steroids; antitubercular drugs were started simultaneously with HRZ in view of positive tuberculin skin test (>15 mm).

The swelling recurred with reduced urine output on the second week of alternate day steroids when the child showed up at our hospital.

There was no history of fever, rash, hematuria, joint pain or swelling. No history of tuberculosis or renal disease in family. Immunisation was as per schedule. BCG scar was present.

On admission, examination revealed bilateral pitting pedal edema, increased abdominal girth and hepatomegaly (2 cm). Development was as per age. Anthropometric measurements were normal.

Investigations showed markedly elevated liver enzymes (SGOT 742 IU/L,SGPT 974 IU/L). Total bilirubin, PT, APTT, INR were normal.

Antituberculous drugs were stopped in view of elevated liver enzymes. Daily prednisolone continued for 2 weeks; edema was increasing progressively; proteinuria was persisting. Oral Frusemide was started, next Spironolactone added. Albumin infusion given in view of low serum albumin and non-resolving edema and proteinuria.

Investigation after 5 days showed significant improvement of liver enzymes (SGOT 38.4, SGPT 52). Isoniazid started according to LTBI protocol.

Patient responded after 3 weeks of daily Prednisolone therapy.

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Discussion

Nephrotic syndrome is a common renal disorder in children. Tuberculosis is endemic in India. Tuberculin skin test is mandatory before starting steroids in nephrotic syndrome. If TST is positive(>5 mm), but the child is asymptomatic and Chest X-ray is normal, Isoniazid should be started and continued daily for 6-9 months. Other options according to LTBI protocol are Rifapentin weekly for 12 weeks or INH + Rifampicin combination for 3 months.

A child receiving ATD may develop drug induced hepatitis. ATD should be stopped if liver enzymes are >5 times normal in asymptomatic child or >3 times normal in symptomatic child. ATD should be introduced gradually, one drug at a time (INH or Rifampicin) following normalisation of liver enzymes.

It is necessary to start ATD in a nephrotic child with positive TST before starting steroids. In a child with positive TST with no symptoms , a normal chest X-ray, Latent Tuberculosis Infection (LTBI) treatment protocol to be followed.

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Out .....! Not Yet....!

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Abstract : *Indian childhood cirrhosis is an entity believed to be gradually going into oblivion.We present the case of a one year old boy presenting with multiple bleeding spots,ascites,hepatosplenomegaly,elevated bilirubin,hypoalbunimia and deranged prothrombin time suggestive of liver disease.Viral, autoimmune, and metabolic etiologies were ruled out by appropriate investigations. Ultrasonography showed chronic liver disease, portal hypertension, and ascites. Due to numerous confounding factors and a low index of suspicion, the diagnosis of Indian childhood cirrhosis remained elusive and was clinched only on liver biopsy.*

Key words : *Chronic liver disease; Indian childhood cirrhosis(ICC); copper toxicity*

Introduction

An infantile and childhood variety of Cirrhosis was first described by Sen from Bengal in 1887. Earlier, it was known by the name 'infantile cirrhosis' or 'infantile biliary cirrhosis', based on a few clinicopathological accounts of the disease. In 1950s, the disease gained public health importance on account of its high prevalence, unique clinical features and high mortality. The pioneer treatise on the clinicopathological spectrum of the disease was compiled and published by a group of expert panellists constituted under the ICMR in mid-fifties[1-4]. In 1960, Achar and colleagues from Chennai proposed a change in name to 'Indian Childhood Cirrhosis' denoting its affliction in young children rather than infants. The etiology of ICC remained unknown, although the role of copper induced toxic injury to liver was hypothesized[5-7].

Case report

A 1 year old male child born out of non-consanguineous marriage presented with symptoms of recurrent bleeding from cracked areas of lips,bleeding from gums and multiple ecchymotic spots over back, chest on and off from 10 months of age. The baby was born by LSCS at term requiring SNCU admission for exaggerated physiological jaundice.Otherwise the gestational period and immediate perinatal periods were uneventful. He had received vitamin K at birth.

There were no complaints of abdominal distension, fever, melena, hemetemesis, yellowish discoloration of eyes, hematuria or trauma.He was breastfed exclusively up to 6 months, after which complementary feeding was started which seemed to be nutritionally appropriate.There was nothing significant in family history.

On examination, he was anthropomerically normal but had moderate pallor. There was no cyanosis,icterus,edema or ascities. Liver was palpable 4 cm below RCM, the span being 7 cm. It was firm, and non tender. Spleen was palpable 3 cm below LCM.

With a clinical impression of possible coagulation defect which could be due to liver disease or congenital factor deficiencies or vitamin K deficiency,he was put through certain investigations. It revealed Hemoglobin level was 7.2 g/dl,TLC 12,300/mm3,platelets 4.3 lac/mm^3,S. Bilirubin 4.6 mg/dl(D-3.1 mg/dl),albumin 3.1 g/dl,globulin 3.1 gm/dl,ALP 370IU/dl,SGPT 89 IU/dl,SGOT 226IU/dl and prothrombin time of 22 secs (INR 1.6).Serum urea, creatininine, electrolytes, urine R/E were normal. Blood and urine cultures did not have any growth.So

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with investigations,pointing towards chronic liver disease, etiological investigations were sought.Hepatitis viral serology and TORCH screen were negative.ANA,anti SMA and LKM and DCT negativity ruled out autoimmune etiology.Serum alpha 1 antitrypsin was normal. Though young age precluded Wilson Disease, serum ceruloplasmin of 46 mg/dl ruled that out also. HIDA scan ruled out cholestasis. Normal tandem mass spectroscopy ruled out other hepatoxic inborn errors of metabolism.

After correction of Prothrombin time by Vitamin K, liver biopsy was done which revealed extensive liver cell necrosis with pericellular fibrosis and sparse regenerative activity with lack of steatosis.There were also diffuse Mallory Hyaline(Fig 1 and 2).Due to lack of facilities, rhodanine staining for copper deposits could not be done.

Early age of onset,characteristic liver biopsy findings and exclusion of other causes of chronic liver disease by appropriate investigations pointed to a diagnosis of Indian Childhood Cirrhosis.

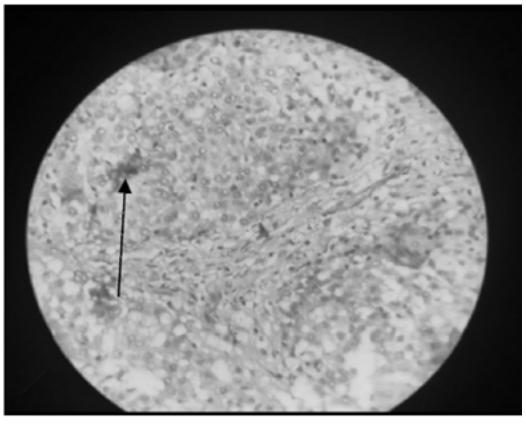

Fig1. HPE showing Mallory Hyaline

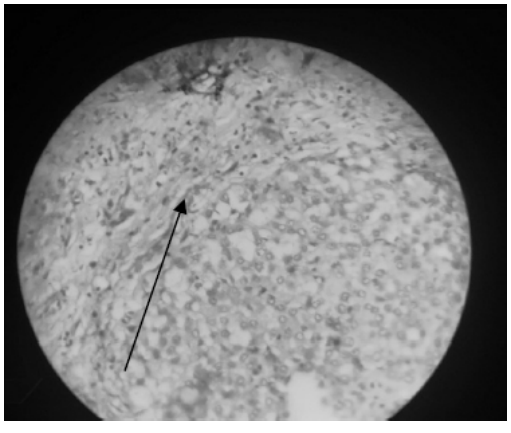

Fig 2. HPE showing effacement of liver architecture

Discussion

ICC became recognized as a distinct clinical entity ever since the landmark identification of its peculiar histological feature: hepatocellular injury accompanied with deposition of intracellular Mallory hyaline similar to that observed in alcoholic liver disease. Copper was implicated in its' etiopathogenesis, when excessive deposits of Orcein positive copper (Cu) and copper-binding protein (CuBP) were seen in the liver of index cases, siblings and close family members. ICC is known for being endemic and unique to India, but there are accounts of published case reports of ICC and ICC-like disease in other parts of the world[1,2].

Studies suggested the hepatotoxic effect of Cu from either domestic water supply or the diet cooked in Cu-yielding utensils. But then, the evidence for the causal role of Cu in ICC was questioned in a study by Sethi, *et al.*[11], who reported no use of Cu utensils in 46% of children with ICC. In a yet another study to explore the association of Cu with liver injury, the authors postulated that an unknown external toxic agent catalyzes hepatocyte injury in genetically predisposed individuals for aberrant Cu homeostasis in infancy[8]. A review of the pedigree charts of families of index cases along with the age-matched controls suggested multifactorial inheritance of the disease[6,7].

A large prospective multicenter study in six centers in India was carried out under the ICMR in 1980's. The results of this research were published nearly two decades later[1]. The authors did not find a significant difference in the use of Cu-yielding utensils among cases with definitive ICC as compared to cases where ICC was ruled out on pooled data analysis. The possible role of an exogenous toxic agent in initiating and perpetuating the hepatocyte injury was suggested instead. The theory behind the toxic insult to the liver originated from the histological presence of Mallory hyaline, which is characteristically observed in cases of toxic injury (like alcohol) to hepatocytes. The authors concluded that Cu deposition is seen as an association with established hepatocyte injury, and hence refuted the role of Cu in triggering ICC. This finding was complemented by epidemiological research from Massachusetts, USA and Germany that failed to find an etiological role of exogenous/

dietary Cu (domestic water supply) in incriminating ICC/ICC-like disease[9-11].

Over the last three decades, there has been a sharp fall in the number of ICC cases and ICC-like diseases. The decline in cases can possibly be either due to a true decline in incidence related to sociodemographic and economic growth or the clinicians are probably unaccustomed to diagnose ICC in the present era. The latter can be explained by an epidemiological upward shift in age of presentation of ICC observed over a period of time. Some of the ICC cases presenting late could have been unrecognized because of the diagnosis of cryptogenic liver disease[10,12].

Conclusion

ICC is uncommon but definitely not extinct. Cases occurring in the post copper utensil era assume significance. The alert clinician must be aware that such cases still exist and the pathologist has a key role to play in recognizing ICC and its variations. Timely biopsy diagnosis, continuous honing of pediatric biopsy skills, infrastructure establishment, and clinician–pathologist communication is essential to improve clinical outcome possibly preventing mortality.

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Spot the Diagnosis: Multiple Bony Swelling Over the Back

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A 6-year-old boy, born of non-consanguineous marriage, presented with multiple bony swellings in the neck and back for last 4 years (Fig 1). Swellings were initially painful, mobile and tender. Later on they became painless, hard and immobile. A few resolved spontaneously. Additionally he had bilateral hallux valgus deformity and restricted movement of cervico-dorsal spines and shoulder joints. Family history of similar disease was negative. Examination of other system including hearing was normal. USG showed multiple intramuscular calcifications. A diagnosis of Fibrodysplasia Ossificans Progressiva (FOP) was made.

FOP also known as 'Stoneman syndrome' or 'Munchmeyer disease' is a rare connective tissue disorder characterized by abnormal and progressive ectopic ossification of the tendons, ligaments, skeletal muscles and other soft tissues of the body. Smooth muscles are not involved. The notable bony abnormalities include bilateral hallux valgus deformity, monophalangic great toes, short and broad femoral necks, pseudo exostoses, short first metacarpal/metatarsals, C2-C7 facet joint fusion. The common differentials of this condition are aggressive juvenile fibromatosis, dermatomyositis, lymphedema, or soft-tissue sarcoma.

Genetic inheritance pattern is autosomal dominant but most cases are sporadic with missense mutation of activin receptor Ia/activin like kinase 2 (ACVR1/ALK2).Exacerbations and remissions highlight the natural course. Flare-ups occur spontaneously or following trauma, biopsy and intramuscular injections. No definitive treatment is there. Corticosteroid, muscle relaxant, analgesics are tried.

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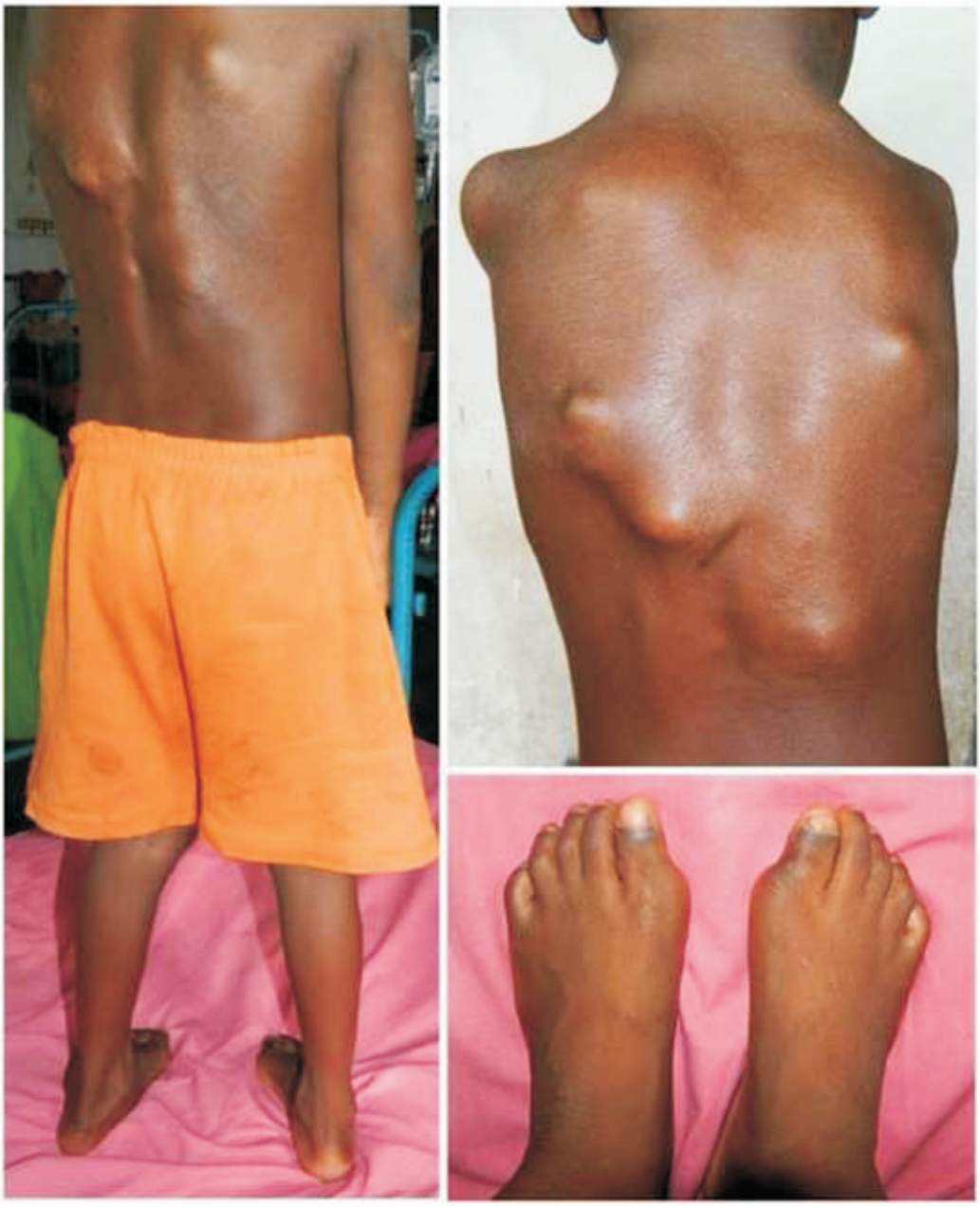

Fig 1: Six year old boy with multiple bony swellings in the neck and back

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