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"Special issue on Pediatric Neurology"

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Karnataka Pediatric Journal

Editorial

Guest Editorial

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Respected members of IAP Karnataka and Readers,

Karnataka Pediatric Journal (KPJ) has over the years occupied an important space in the field of pediatrics in Southeast Asia and across. It gives me an immense pleasure to be a guest editor of this reputed journal.

KPJ has provided an outlet to talented clinicians across Karnataka to share their clinical and research work across medical fraternity, this edition is a special edition covering the domain of neurology and bring across experts in this field with topics relevant to office-based pediatrician on a day-to-day basis and also to colleagues who have special interest in the neurology.

The first topic from Dr. Saha and colleagues from Dhaka examines the issues and controversies surrounding the management of febrile seizure, a common clinical condition with varying lines of management, we hope this article will help in clarifying role of prophylaxis clobazam in prevention of recurrence and clarifying no role for anti epileptic drugs as a routine

Dr Surana and Dr Pujar and colleagues speak about the management of status epilepticus and its long-term morbidity and mortality. Dr Pujar has done his PhD on the topic of long term sequalae in status epilepticus, and he shares his insight on risk of mesial temporal lobe sclerosis and risk factors that can lead significant morbidity and mortality following to convulsive status epilepticus (CSE)

EEG is an often used and abused test in the field of pediatric neurology, Dr Asim Shahid, Epileptologist from Cleveland shares the many benign variants that often baffle a EEG reader, often these benign variants are over read as abnormal leading to medicating children unnecessarily which is apart from the stigma and hassles parents have to face in long term follow up!

MRI is easily accessible these days and often requested in children with any neurological disorders, Dr Kamble, Neuroradiologist from Aster Hospitals, Bengaluru, sheds light on varied sequences that yields better information in facilitating diagnosis. MRI in children is demanding in sedation, co-ordination and convincing parents, hence it helps to get it right first time, hope this article helps in choosing the right imaging. Dr Kamble emphases MRI scanning is a dynamic process which requires active engagement between the treating clinician and reporting radiologist to plan sequences and also adapt sequences once initial images are completed.

As medicine evolves, newborn screening (NBS) is to become a norm, which is routinely done in major cities, however there is still a huge vacuum in infrastructure and expertise in interpreting these tests, Dr Anil Jalan who is a walking encyclopedia in metabolic medicine sheds light on the cost advantage and effectiveness of NBS.

Dr Sankhyan and Dr Bhagwat from PGI, Chandigarh essay on an absorbing topic of Vitamin responsive conditions which is not only intriguing to our mind, but also highlights there are many disorders which if investigated and treated in time leads to an excellent outcome. Infantile tremor syndrome commonly known as ITS is often mis-diagnosed as seizure, whereas this condition responds to mega doses of Vitamin b12 and is completely reversible. Similarly, pseudo paralysis caused by Vitamin C deficiency, biotin thiamine-responsive basal gaglia disease is some of the reversible condition this article sheds light on.

Finally, this edition closes with fine case reports from Dr Lokesh Saini who head the division of paediatric neurology at AIIMS Jodhpur on dystonia management which is an uncommon presentation, and Dr Vykuntaraju from Indira Gandhi Institute at Bengaluru shares a case of sodium channel mutation presenting with epileptic spasms.

This interesting compilation of topics will surely stimulate the minds and hope it adds value to your day-to-day practice.

I wish to gratefully acknowledge authors for sparing time, Dr. Bidisha Banerjee, Consultant Paediatric Neurologist, Manipal Hospital, Bengaluru; Dr. Sithara Ramdas, Consultant Paediatric Neurologist, Oxford; Dr. Rashmi Adiga, Consultant Paediatric Neurologist, Rainbow Children's Hospital, Bengaluru; Dr. Mahesh Kamate, JNMC, Belagavi, and finally, Editor-in-Chief Dr. Bhaskar Shenoy for considering to bring this special edition.

With best wishes

Ravi

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Karnataka Pediatric Journal

Review Article

Clinical review of febrile seizure and updates

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ABSTRACT

Febrile seizure (FS) is one of the most common seizures seen in infant and pre-school age. There are two types of FSs, simple and complex. Simple FS are commonly benign, but complex FS have long-term effects. Most children with FS have normal growth and development after the attack; however, recent evidences suggest that a small group of children presenting fever with seizure may subsequently develop epilepsy or recurrent seizures. Diagnosis is mainly based on clinical presentation, electroencephalogram, lumbar puncture, and neuroimaging, which can be applied based on clinical scenario, but not routinely. Treatment is principally acute management of seizure along with address of underlying etiology and intermediate prophylaxis for preventing further attack. Pediatrician should be familiar with the proper diagnosis and management of this condition. This review will highlight an update on the current diagnostic and management issues of FS.

Keywords: Febrile seizure, Anticonvulsant, Epilepsy, Management, Febrile status epilepticus

INTRODUCTION

Febrile seizure (FS) is one of the most common types of seizure in children. It is usually defined as seizures occurring in children (6 months to 5 years of age) in association with a fever more than 100.4°F (38°C), who have no evidence of any intracranial cause (e.g., head trauma, infection, and epilepsy), or any underlying definable cause of seizure (e.g., hypoglycemia, dyselectrolytemia, and drug withdrawal), or any history of an afebrile seizure.[1-4] ILAE defines FS as a seizure occurring in children aged at least 1 month, associated with a fever which is not originated by any infection of the central nervous system (CNS). A child diagnosed with FS must not have a previous unprovoked seizure, neonatal seizure, or any acute symptomatic seizures.[5] National Institute of Health, USA consensus conference definition of FS illustrates an event typically occurring between 3 months and 5 years of age associated with febrile illness without any evidence of intracranial infection or defined causes.[6] Thus, there is variability of age in different current definitions.

FS is subdivided into two categories: Simple FS and complex FS [Table 1]. Simple FS is more common than complex FS, accounting for more than 70%.[7] Febrile status epilepticus (FSE) is a subgroup of complex FS accounts for 5% of all FS, which are prolonged, continuous, or intermittent seizures without consciousness procured and evolve into status epilepticus.[7,8]

FS is an utmost challenge in pediatric practice due to its high prevalence and tendency to recur. Updated guidelines for diagnosis and treatment of FS have been issued by the American Academy of Pediatrics (AAP) and the Japanese Society of Child Neurology in 2011 and 2015, respectively.[9,10] PubMed search did not find any more guidelines on FS as of publication of this review.

Table 1: Characteristics of simple versus complex FSs.[9]

Character	Simple FS (all of the following)	Complex FS (any of the following)
Age	6 months to 5 years	6 months to 5 years but may be younger age
Types of seizures	Generalized	Focal
Duration of seizure	Less than 15 min	Prolonged, (≥15 min)
Occurrence	Once in 24 h	Recurs within 24 h
Associated neurological condition	No previous neurologic problem	Developmental delay or focal neurologic signs
Post-seizure complication	No postictal pathology	Todd's paresis may be present, seizure may persist for>30 min

FEBSTAT STUDY

Consequences of Prolonged FSs (FEBSTAT) was a prospective multicenter study that assessed the relationship between prolonged FSs and acute hippocampal injury, progress to mesial temporal sclerosis, temporal lobe epilepsy, and hippocampal impairment. The study enrolled 199 children of 1 month to 5 years age who had a FS that persisted more than 30 min.[11,12] Most of the children had focal seizures that were generally first FSs. Human herpes Virus (HHV)-6B infection is commonly associated with FSE and HHV-7 infection was less frequently related with FSE.[13] Younger age and developmental delay were associated with prolonged FS.[14] FSE seldom terminated spontaneously, was fairly resistant to drugs, and even with treatment continued for a significant period of time. Prompt initiation of treatment results in shorter total seizure duration.[15]

The study was established, FSE seldom causes cerebrospinal fluid pleocytosis.[16] The study inferred that electroencephalogram (EEG) findings within 72 h of FSE (focal slowing or attenuation) might be used as a sensitive marker of acute injury linked with FSE.[17] Developmental abnormalities of the hippocampus especially hippocampal malrotation were more frequent in the FSE group.[18] Risk for a subsequent FSE was remarkably increased in FSE versus simple febrile seizure (SFS). Magnetic resonance imaging (MRI) abnormality might increase 3.4-fold ($P < 0.05$) risk of FSE and also increased the recurrence risk when FSE was compared to SFS.[19]

Search strategy

A PubMed, Cochrane, ILAE, and different guidelines searches were conducted in November 2020 using the key terms "FSs" and "febrile convulsions." The search strategy covered meta-analyses, randomized controlled trials, systematic reviews, and observational studies.

EPIDEMIOLOGY

FS is the most frequently found neurological disorder, affecting 2–5% of children between 6 months and 5 years of age in the Western Europe and United States with an optimum incidence between 12 and 18 months.[4,9,20-23] However, most FS (90%) occur within the 1st 3 years of life.[24] Although FS is seen in all ethnic groups, it is more commonly seen in Asian population (5–10% of Indian).[25] The male-to-female ratio is roughly about 1.5–1.8:1.[22,26,27] The majority of FS occur within 24 h of onset of fever. FS often occur in the evening, peaking between 6 pm and 10 pm and most frequently in winter, and least frequently in summer.[28-31]

ETIOLOGY AND PATHOGENESIS

FS is an age-dependent response of immature brain to fever.[32] The exact etiology is still undetermined, though possible causal relationship with genetic and environmental factors have been reported [Figure 1].[33] Releasing high levels of cytokines like interleukin 1 and tumor necrosis factor during a fever may alter normal brain physiology including certain temperature sensitive ion channels, triggering seizures.[34] Developing brain especially under 3 years has inherent increased vulnerability to neuronal excitation and low seizure threshold that explains high fever related seizure burden in children.[31]

Various patterns of inheritance have been demonstrated, for example, an autosomal dominant inheritance with reduced penetrance and a polygenic or multifactorial inheritance.[2,29,35-45] The concordance rate in monozygotic and dizygotic twins is about 35–69% and 14–20%, respectively. The genes and loci of chromosomes that might increase the risk of developing FS have been mapped [Table 2].[33,46]

FS may develop due to mutations in the gene that encodes for the γ-aminobutyric acid A receptor and sodium channels.[36] Mild loss of function or polymorphisms in *SCN1A* gene of $Na_V1.1$ channels may cause a remarkable portion of FS.[47] This mutation depletes peak sodium current for positive shift in the voltage dependent activation when expressed in non-neuronal cells.

Perinatal stress and exposure to nicotine and/or alcohol may potentiate FS due to increase in cortisol level in the offspring.[48-50] Approximately 80% of cases of FS are related with viral infection and the most frequent infections are middle ear infections, tonsillitis, sinusitis, pneumonia, bronchiolitis, tooth infections, and gastroenteritis.[51-53]

Although vaccine is generally well-tolerated, transient adverse events such as FS are rarely experienced after vaccination.[54] FS usually occur within 3 days after Diphtheria, tetanus toxoids and whole-cell pertussis vaccine, 2 days after Pneumococcal conjugate vaccine 7 vaccine, and

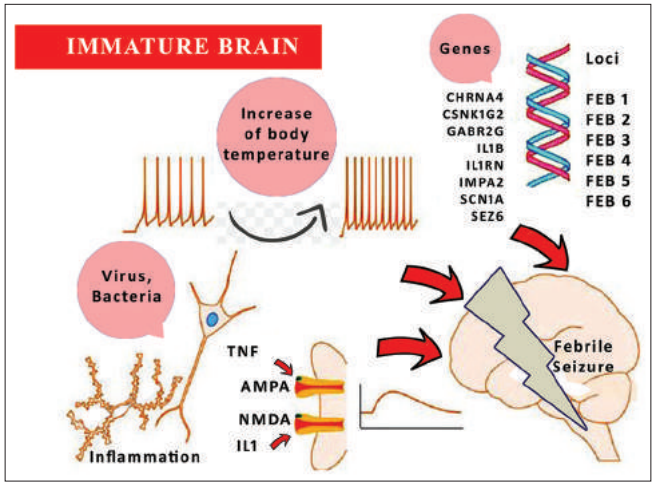

Figure 1: Mechanism of febrile seizure.[33]

Table 2: Different mutations and their clinical correlations.[33,46]

Gene	Loci	Chromosome	Clinical synd romes
GRCH38	FEB1	8q13-q21	FS
	FEB2	19p13.3	FS(Most common)
SCN1A	FEB3A	2q24	Simple FS
ADGRV1	FEB4	5q14-q15	FS
AKAP18		6q22-q24	Simple FS
GABRG2/ C588Tgene gene, encoding the GABA (A) subunit receptor	FEB8	5q34	Febrile convulsion with or without absence seizure
Interleukin 1 beta (-511)		1q31.	Increase frequency of FS (IL-1 beta-polymorphism)
IFI44L		1q31	FS
TMEM16 family gene		12q21.33	FS

FS: Febrile seizure

24 h after Measles Mumps Rubella vaccine.[55-58] Diphtheria, tetanus and acellular pertussis vaccine has fewer chances of FS compared to whole-cell vaccine as it contains minimum number of proteins which does not induce the IL-1â Production (Box 1).[59,60]

RISK FACTORS

The average risk of recurrence is 33%.[61] The major risk factors for recurrence are positive family history, the first FS under the age of 18 months, and 1st episode of complex FS.[4] It has been illustrated that the peak temperature in lieu of the rapidity of the temperature upraise is the most remarkable risk factor for developing first FS.[21,31,62-65] However, the number of FS does not alter the risk of subsequent epilepsy.

Iron is essential for certain neurotransmitters function and thus iron-deficiency anemia may predispose FS.[52,66] In a Bangladeshi study, the authors have showed that mean Zinc concentration in both serum and CSF was significantly lower among children having FS than their matched non-FS peers. Hence, Zinc deficiency is identified as a risk factor for FSs.[67-69] Low serum Vitamin B12 and folic acid level decrease a child's threshold for seizure and may be a risk factor for FS and recurrent FS.[66] Road traffic noise and air pollution during childhood are related with a bit higher risk for FSs, following a compressed exposure–response link.[51] Traffic noise closely associated with stress and sleep disturbance which may be assume mechanisms beyond a relation with increase vulnerability to viral infection. Air pollution exposure is connected with upper airway infection. Some authors mentioned that few risk factors are responsible for developing FS, recurrent FS and also described the chance of subsequent epilepsy in various seizure semiology (Box 2, 3).[70-75]

CLINICAL EVALUATION

In most cases, FS occur within 24 h of the fever.[53] Seizures occurring for more than 3 days after the onset of fever should be suspected for other differentials.[76] Loss of consciousness with breathing difficulty, pallor, or cyanosis at the time of seizure is a common feature.[77] Atonic and tonic spells have also been reported.

A detailed history should be obtained to evaluate the cause and characteristics of fever including fever onset to the occurrence of seizure, duration and the peak temperature of fever, duration of postictal drowsiness, and seizure semiology. The history should also comprise prior seizure and whether the child was recently attended day care, vaccinated, or treated with an antimicrobial agent. Immunization status, developmental milestones, CNS trauma, potential exposures to infection, toxin ingestion, and history of febrile and afebrile seizures among any family member(s) should also be inquired.[23] If postictal drowsiness is unusually prolonged, one should rule out CNS infection in addition to other features that may be related to meningoencephalitis.

A thorough physical assessment must be done to evaluate the cause(s) of the fever. A reddish bulging eardrum, exanthem, a beefy red pharynx, swollen, and erythematous tonsils may give hint to the fever etymology. The assessment should look for depressed sensorium, irritability, lethargy, bulging or tense fontanel, nuchal rigidity and Brudzinski's or Kernig's sign to exclude CNS infection such as meningitis or encephalitis.[78] A sequential neurological assessment should also be performed, comprising the level of consciousness, muscle power and tone, and deep tendon reflexes. Any focal sign should pay due attention. Fundoscopy should be done to rule out papilloedema.

LABORATORY INVESTIGATIONS

Blood for complete blood count, electrolytes, calcium, phosphorous, magnesium, glucose, urea, creatinine, and bacterial culture are usually not helpful in evaluating a child with FS but required for identification of cause depending on clinical presentation.[8,79] The laboratory investigations should be individualized based on the history and physical examination.[3,9,80]

Lumbar puncture (LP) is not essential in the majority of well-appearing children who have rapidly returned to quite normal baseline activities, or having no lethargy, neurological deficit after post-ictal period.[4] The AAP strongly urges pediatricians to consider a LP in child with FS in following situtions:[2,3,5,81,82]

1. Less than 12 months of age who present with FS, especially if the vaccination status for *Streptococcus pneumoniae* and *Haemophilus influenzae* is deficient or unknown
2. Younger than 6 months with a simple FS
3. At any age: Altered alertness, lethargy, and/or meningeal symptoms or FSE
4. Occurrence of seizure after the 2nd day of fever, who have taken prior antimicrobial therapy.

EEG has limited value to predict recurrent FS.[5,8,21] A routine EEG is not recommended to evaluate neurologically healthy child with a simple FS.[8,10] A 2017 Cochrane systematic review also found no diagnostic value of EEG and its timing after complex FS.[83]

An EEG should be considered in children with FS who have[4,53,84,85]

1. Complex FSs, especially those with multiple or prolonged seizures
2. Recurrent FSs with developmental delays.

EEG showed bilateral posterior slow wave activity in as much as 80% of cases when done on the same day of the seizure, which usually disappears by 7–14 days.[86] Although EEG abnormalities may persist over several years, yet none of these abnormalities have been associated with increased risk of recurrent FS or future development of epilepsy.[87]

Neuroimaging studies such as computed tomography (CT) and MRI of brain are not routinely indicated in children with FS.[20,21] MRI or CT should be performed in children with signs of-[4,22]

1. Raised intracranial pressure or abnormally large heads
2. Suspected structural defect in the brain, focal neurologic abnormality, and severe head injury
3. Neurodevelopment abnormality
4. FSE.

COMPLICATIONS

FS can be extremely panicked and emotionally traumatic for parents, though no association exists between FS and sudden unexplained death in childhood.[1,4,5,88-90] The seizure may be associated with postictal transient hemiparesis (Todd's palsy) or may have a prolonged period of postictal drowsiness.[2,22,69] Recurrent and prolonged FS may cause persistent alternations of hippocampal neuronal circuits or mesial temporal sclerosis, leading to refractory temporal lobe epilepsy.[1,14,88,91-92]

DISEASES THAT INITIALLY MAY PRESENT WITH SEIZURE PRECIPITATED BY FEVER[93-96]

Rare exceptional cases who presents with fever precipitated seizures should be evaluated critically with clinical evidence and if required by molecular study like clinical Exome sequencing for following diagnostic possibilities:

1. Generalized/genetic epilepsy with FSs plus
2. Dravet syndrome – suspects are prolonged febrile hemiconvulsive seizure and photosensitivity on EEG under 2 years of age.
3. New-onset refractory status epileptics
4. Febrile infection-related epilepsy syndrome
5. Hemiplegia Hemiconvulsive syndrome.

Above mention differentials should be excluded from FS and manage carefully in suspected scenario.

MANAGEMENT: COMMUNITY SETTING

Parents should be counseled about benign nature and favorable outcome, assure them that treatment is often unnecessary and rare association of simple FS with epilepsy.[26] In this context, organizing effective awareness programs for parents can be helpful.[3,83,88]

MANAGEMENT: AT HOSPITAL SETTING

Treatment should be initiated with intravenous (IV) lorazepam or diazepam if the seizure is still ongoing and repeat the dose if required [Table 3].[2,24,97,98] Per-rectal diazepam and buccal or intranasal midazolam should be administered as safe and effective alternatives, when IV route is unavailable or inaccessible.[3,24]

FSE often requires multiple antiepileptic medications to control as it is rarely stopped spontaneously.[15,24] If the seizures continue for 10–15 min, phenytoin or phenobarbital can be given intravenously [Table 3]. An additional dose of IV phenytoin should be given 10 min after the loading dose, only when seizures fail to stop. Howbeit, IV phenobarbital, valproic acid or levetiracetam can also be given alternatively.[98] In addition, the cause of the fever must be treated accordingly whenever possible.

Table 3: Emergent initial therapy for acute (ictal) management of FS in children.[3,8,35]

Antiepileptic	Administration route	Dose
Midazolam	Oral	0.5 mg/kg BW, repeat in 10 min if necessary
	Nasal	0.20.5 mg/kg BW divided in each nostril, maximum 10 mg
	IV	0.2 mg/kg BW or 0.15 mg/kg BW by infusion
	Intramuscular	0.2 mg/kg BW or 510 mg, buccal dose
Diazepam	Rectal	0.30.5 mg/kg BW, max 10 mg, bolus speed of 5 mg/min, repeat in 10 min if necessary
	IV	0.1–0.2 mg/kg BW, 0.01 mg/kg BW/min by infusion
Lorazepam	IV	0.1 mg/kg BW (maximum 4 mg in children heavier than 40 kg)
Phenytoin	IV	20 mg/kg BW, if required, repeat 5–10 mg/kg BW
Phenobarbital	IV	20 mg/kg BW, if required, repeat 20 mg/kg BW
Valproic acid	IV	20–40 mg/kg BW
Levetiracetam	IV	20–60 mg/kg BW

BW: Body weight

As per AAP recommendation, clinically stable children older than 18 months should not be hospitalized; rather parents should be trained for home management [Box 5].[37,99] Besides, previously diagnosed children with recurrent FS also do not require hospitalization [Table 1].[26,39]

Hospital admission should only be considered to children in following conditions:[24,77]

1. Suspicion of any serious infection
2. Who have prolonged and/or focal seizures, particularly if there is residual neurological findings or delayed recovery to baseline
3. Less than 18 months of age, for observation and possible LP.

PREVENTION OF FURTHER ATTACK

A Cochrane systematic review (2017) stated that daily administration of Phenobarbital, valproic acid or other antiepileptic drugs are effective in the prevention of FS.[2,22] The potential adverse effects of these drugs outweigh their benefits.[5] Therefore, continuous prophylaxis with anticonvulsants is not necessary for simple or complex FS.[5,21,24] Furthermore, the AAP does not recommend continuous antiepileptic therapy with valproic acid or Phenobarbital for recurrent FS prevention.[5]

Box 1: Cause and factors associated with febrile seizures.[35,48-53]

Familial: Genetics [Table 2]	Channelopathies: Sodium (mainly) potassium and calcium channels GABA-A
Viruses: Influenza and Parainfluenza virus, Respiratory syncytial virus, Adenovirus, Herpes viruses, Cytomegalovirus, Chickenpox, Corona virus, Rotavirus, and Entero viruses.	Vaccination: Diphtheria, tetanus toxoids and whole-cell pertussis, Pneumococcal conjugate vaccine 7, Measles Mumps Rubella Cytokines: IL 1, tumor necrosis factor
Bacteria: *Escherichia coli*, *Shigella dysenteriae*, *Streptococcus pneumonia*, and *Salmonella enteritidis*	Vitamin (Vitamin B12) and folic acid
Maternal: Antenatal maternal stress, prenatal exposure to nicotine and/or alcohol Environmental: Exposure to traffic noise and air pollution	Neonatal: Prematurity, hypoxic ischemic encephalopathy, Postnatal treatment with corticosteroids, Neonatal brain injury Cerebral dysgenesis

Intermittent Prophylaxis: Intermittent administration of diazepam (0.3–0.5 mg/kg/dose 8 hourly, maximum 10 mg) or oral clobazam (1 mg/kg once daily, maximum 20 mg) at the onset of fever for initial 3 days has been shown to be effective in recurrent FS prevention in 80% of cases.[5,100,101] Some studies concluded that intermittent clobazam therapy seems more beneficial to diazepam due to similar efficacy, long half life time, and lower side effect such a drowsiness, sedation, and ataxia.[102,103] Besides, intermittent therapy may also be considered in those at high risk for recurrence and in high parental anxiety, especially with a history of multiple and/or prolonged FSs.[3,5,10,24]

Acetaminophen and Ibuprofen are effective antipyretics to relieve fever, though antipyretic agents do not minimize the risk of a FS or a seizure recurrence[2,27,104] Notwithstanding, no evidence was found to be effective to prevent recurrent FS through physical methods of temperature reduction (e.g., direct fanning of the child, tepid sponging, removing clothing, and cooling room).[10,20,29] Universal childhood vaccinations should be strongly encouraged to reduce the risk of FS in the coming years. However, prophylactic antipyretic prior vaccinations are not statistically indicated to reduce the rate of FS recurrences.[100]

PROGNOSIS

The prognosis is favorable in the majority cases as it is typically benign and self-limiting.[24] Usually, children surpass this condition by 6 years of age. About one-third of FS will have a recurrence during early childhood, wherein only <10% will have ≥3 recurrences.[22-24,26] Approximately, 90%

Box 2: Risk factors for the first FS, recurrent FS, and epilepsy after FS.[2,21,31,35,63,65,70-74]

First FS	Recurrence after 1st attack of FS	Epilepsy after FS
In Population i. 1st or 2nd degree relative with history of FS (20% affected sibling and 33% affected parents) ii. Neonatal nursery stay of>28 days iii. Developmental delay In Children with a febrile illness iv. 1st or 2nd degree relative with history of FS v. High peak temperature	i. Age<18 months ii. Family history of FS iii. Low peak temperature iv. Attendance at day care v. Less than 1 h of fever prior the seizure vi. Frequent febrile illnesses vii. Multiple FSs during the same febrile illness viii. Neurodevelopmental delay	i. Shorter duration of fever (<1 h) before the seizure ii. Onset of FS before 1 year or after 3 years of age iii. Neurodevelopmental abnormality iv. Complex FS v. Family history of epilepsy vi. Low Apgar at 5 min at birth vii. Epileptiform discharges on EEG

FS: Febrile seizure

Box 3: Spectrum of febrile seizure and chance of subsequent epilepsy.[8,21,31,53,75]

	Chance of epilepsy
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures	6%
Family history of epilepsy	18%
Neurodevelopmental abnormalities	33%

Box 4: Initial management of FS at home.[2,7,8]

1. Remain calm, no panic, loosen clothes, secure the child from injury
2. Do not introduce fingers or objects to open the mouth or to give any drugs or fluids
3. Do not recommend to wet the child during the seizure
4. If unconscious, to decrease the risk of aspiration, place the child in lateral position
5. Once the seizure is controlled, make sure that child is in lateral position to quicken recovery without obstructing airway
6. In recurrent FS, administer initial rescue therapy if seizure lasts>5 min
7. Administer per-rectal diazepam or nasal/buccal midazolam as first line treatment [Table 3]
8. Seek hospital admission if the seizure lasts>5 min or more
9. A medical intervention is crucial in the following cases: (a) Seizures duration of>15 min or not revoking after treatment, (b) Recurrent seizures, (c). Focal seizures, (d) presence of prolonged consciousness and/or postictal palsy

FS: Febrile seizures

recurrences occur within 2 years wherein 75% happen within 1 year.[26,53] Children without any of the above mentioned risk factors are accounted for only 4% chance of recurrence, whereas those with all of the risk factors have up to 80% chance of recurrence (Box 2).[21,24] The majority of children with simple FS have normal growth and development but complex FS and FSE may turn into epilepsy.

Box 5: Febrile status treatment in a hospital environment.[80,100]

1. Open the airway, aspirate secretions, maintain adequate ventilation, and ensure perfusion
2. Obtain venous access
3. Monitor vital signs
4. Oxygen supplementation, if necessary (SpO_2 < 92%)
5. Administer diazepam intravenously or per-rectal
6. Monitor arterial blood gas analysis, electrolytes and blood glucose
7. If convulsion does not subside, ask pediatrician to determine treatment options
8. FSE should be treated under the same treatment guideline for pediatric a FSE
9. The measures for fever reduction must be taken after benzodiazepine administration.

COUNSELING

FS in children can give rise to significant parental anxiety and fear of the death of their child. It can be alleviated by regular educational programs by specialized health workers to explain the benign nature of the condition and lack of any significant association with future epilepsy.[24,44] It is important to teach about home management and basic resuscitation measures to every parent who has children with febrile convulsions.[5,24]

CONCLUSION

Worldwide, FS is one of the most common age-dependent seizures, especially in South Asia. FS has genetic predisposition with a notable vulnerability of the developing brain to the effects of fever. Almost one-third of children have chances of recurrence, but they outgrowth the condition after 5 years of age. Although continuous anti-epileptic therapy can prevent recurrent FS and surpass the few risks of FS, yet it cannot prevent subsequent epilepsy. Besides, it has high potentiality for adverse effects. Hence, long-term therapy

is not recommended. However, intermittent therapy with diazepam or clobazam at the onset of fever may be advised to prevent recurrent FS in high parental anxiety and/or multiple recurrences of FS. Prolong seizure must be treated acutely. Parental counseling on home treatments and about the risks associated with FS is the greatest contribution that the pediatrician can make for the care of children with FS.

Key message

- FS has slightly male preponderance.
- Usually autosomal dominant in inheritance.
- Low age at onset for FS has appeared a crucial predictor for a repeated FS.
- Simple FS are common, benign, and self-limited.
- Children with complex FS are at risk of developing epilepsy.
- FS usually does not cause intellectual or neurologic damage.
- EEG and neuroimaging are not indicated in the routine evaluation of simple FS.
- Acute treatments are indicated when seizure is prolonged.

Limitations

While the review contains updated clinical recommendations, still there are many unanswered or controversial problems. Many limitations might be due to the lack of conclusive clinical evidences, particularly regarding the prophylactic use of intermittent drug in FS, and FSE. Future clinical research is required to explain these unanswered questions. Howbeit, this review may play a role in raising issues in the treatment of FS and in prompting further investigations or research.

Author contributions

Hossain MM. wrote the first draft of the manuscript; Saha N critically revised the text and made substantial scientific contributions. Both the authors approved the final version of the manuscript.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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There are no conflicts of interest.

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Review Article

Long-term prognosis and predictors of outcomes after childhood convulsive status epilepticus

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ABSTRACT

Objective: Childhood convulsive status epilepticus (CSE) is widely known to be associated with short-term and long-term mortality and morbidity, but the role of CSE itself on adverse outcomes is debatable. The additional effect of CSE characteristics on outcomes after CSE and whether prolonged seizures cause any long-term hippocampal injury which leads to developmental or memory impairment is uncertain. This review provides an overview of long-term prognosis after childhood CSE, highlighting data from recent literature.

Findings: In previously normal children, the long-term prognosis after childhood CSE is favorable, with low incidence of epilepsy, motor, and cognitive difficulties. Mesial temporal sclerosis is uncommon in children after prolonged febrile seizures. In children with symptomatic causes and those with pre-existing neurological abnormalities, there is substantial morbidity after childhood CSE. Etiology is the primary determinant of outcome after childhood CSE and the additional effect of CSE characteristics such as seizure duration seems to be less than previously believed.

Keywords: Childhood, Status epilepticus, Prolonged febrile seizures, Long term, Prognosis, Outcomes

INTRODUCTION

Convulsive status epilepticus (CSE) is the most common medical neurological emergency in children, with an overall estimated incidence of 20/100,000 children per year.[1-3]

The definition of CSE has evolved over time, with the commonly used definition of CSE as a seizure lasting for a duration of 30 minutes or longer. Recently, the International League Against Epilepsy Task Force on classification defined status epilepticus (SE) as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures."[4] The Task Force reached a consensus opinion that time point t1 (time for initiation of treatment) should be at 5 min and time of t2 (indicating the potential threat of brain damage in humans after this time point) at 30 min for generalized convulsive seizures, and t1 of 10 min and t2 of >60 min for focal SE with impaired consciousness.[4]

In a landmark study published in 1970, Aicardi and Chevrie reported the outcome of CSE in children as "grave, mental, or neurological residua or both being present in at least 57% of patients."[5] Subsequent prospective studies, however, have reported better outcomes.[6] This may

be a reflection of improvements in emergency management and intensive care for children presenting with CSE and also a reduction in the incidence of bacterial infection-related acute symptomatic seizures as a result of universal immunization in recent decades. The long-term sequelae after childhood CSE may include neurological, cognitive, and behavioral impairments and impact on quality of life.[7,8] However, the role of CSE itself on the sequelae and whether the outcomes are influenced by the underlying etiology, patient's age, the type of CSE, and duration of CSE is debatable. Furthermore, while there is some evidence to suggest that prolonged febrile seizures (PFSs) may result in short-term hippocampal injury leading to developmental or memory impairments, whether these changes then lead to the development of mesial temporal sclerosis (MTS) and/or temporal lobe epilepsy (TLE) is uncertain.[7,9-11]

The aim of this review is to provide an overview of the long-term prognosis and the predictors of adverse outcomes following childhood CSE.

LITERATURE SEARCH

We performed a search on PubMed for original articles published up to November 30, 2020, with the search term "status epilepticus" combined with the terms "prognosis," "outcome," "mortality," "fatality," "death," "morbidity," "recurrence," "cognition," "MTS," "hippocampal sclerosis," and "quality of life." The search was also done with the terms "prolonged febrile seizures" and "prolonged febrile convulsion." The references of identified articles were examined for additional relevant studies. We only included the studies reported in English and included patients between the ages of 1 month and 18 years at the time of SE.

PROGNOSIS IN CHILDREN AFTER CSE

It is widely known that CSE is associated with increased mortality and morbidity. The long-term adverse outcomes reported in children that have previously had childhood CSE include epilepsy, MTS, CSE recurrence, motor and/or intellectual disability, behavioral impairments, and impact on quality of life.

MORTALITY

Short-term mortality

Short-term or immediate mortality in CSE is defined as mortality within the first 30 days after SE. In studies reported before the year 2000, the short-term mortality rates were ranging from 3% to 9%, whereas after 2000, the rates are significantly lower, with the more recent studies reporting rates below 1%.[1,12-15] The lower rates in the newer studies are most likely due to the advances in intensive care and out-of-hospital emergency management of CSE and the reduction in the incidence of CSE due to acute symptomatic causes such as bacterial meningitis. Furthermore, it is important to bear in mind that most of the older studies of CSE do not specifically investigate children. CSE associated mortality increases with age in adults and hence can result in a higher case fatality rate in these studies.[16,17]

Long-term mortality

The cumulative mortality rates range between 5.4% and 13% within 10 years after CSE as reported in population-based studies.[18-21]

A prospective pediatric population-based study from North London, United Kingdom, reported an overall case fatality rate of 11% within 8 years after CSE. Among 226 children in the study, 7 (3%) died within 30 days of CSE and 16 (8%) died during follow-up.[1,21] A more recent retrospective hospital-based study followed up 460 children for a median duration of 63 months reported mortality of 3.8%.[22]

Risk factors for death

In the North London study, the majority of deaths were as a result of complication of their underlying medical condition, while in about a quarter, the deaths were associated with either CSE or intractable epilepsy. The main risk factor for mortality was the presence of pre-existing clinically significant neurological impairments. Of note, no deaths were reported following idiopathic CSE and PFS, which is consistent with previous reports suggesting that SE in itself may be less harmful.[21]

There are several studies which report higher risk of death in children <1 year of age[7,18,23] while some other studies have shown no association between age and mortality.[15,21] The higher prevalence of death in younger children below 1 year of age may indicate the high incidence of acute symptomatic CSE in this age group, in keeping with previous observations of higher mortality due to acute symptomatic etiology. Although in some studies, a direct association between longer duration of CSE (>24 h) and higher mortality has been reported, it is highly likely that longer duration of CSE is a marker of the severity of underlying cause which increases the risk of death.[18,24]

Therefore, death in children with CSE is most likely due to complications of their underlying brain disorder rather than due to prolongation of seizure.

SUBSEQUENT EPILEPSY

The risk of subsequent epilepsy 2 years after the first episode of unprovoked CSE is 15–40%, which is similar to the risk of seizure recurrence after first self-limited short unprovoked

seizure.[7,25-27] In the North London study, in children with CSE, the cumulative incidence of epilepsy was 24.7%, with nearly 90% occurring within 18 months of CSE.[27] Focal epilepsy is the most common type. Unilateral CSE with slight fever could be initial presentation of Dravet syndrome or a focal structural lesion.[5,28,29] The incidence of subsequent epilepsy, however, varies depending on the cause of CSE. In the North London cohort, the incidence of subsequent epilepsy was 14.3% after PFS, 13.3% in acute symptomatic CSE, 45.5% in remote symptomatic, and 50% in unclassified CSE. Absence of fever was the only significant predictor of incident epilepsy with an odds ratio of 7.5 (95% confidence interval 2.25–25.1).[27]

Overall, the long-term risk of developing epilepsy after PFS or febrile CSE ranges between 4% and 15%.[19,27,30-32]

The hypothesis that PFS or febrile CSE has a causal role in the development of MTS and associated TLE is derived from retrospective studies from tertiary epilepsy centers (thus potentially subject to selection bias).[33-36] However, prospective and population-based studies have failed to demonstrate a causal association.[19,31,37-40] Although prolonged seizures may result in acute hippocampal injury, there is not sufficient evidence to suggest that this results in long-term consequences such as MTS and/or TLE.[7,9,11,27,41-44] Overall, there is low incidence of TLE (<6%) and MTS (<7%) after PFS which implies that although PFS might increase risk of hippocampal injury in those with pre-existing abnormalities, the direct contribution of PFS in development of MTS, TLE, or both seems less than has long been believed.[9,11,27,31,43-45]

RECURRENCE OF CSE

The estimated overall risk of recurrence of CSE in children ranges between 10% and 70.5%.[7,22,27,46] The risk of CSE recurrence within 8.9 years was 43.3% due to all causes of CSE in the North London study.[27] In another retrospective hospital-based study from the United States, the recurrence rate of CSE was as high as 70.5% with a median follow-up period of 63 months, which may be due to the study design and recruitment bias.[22]

The main risk factor for CSE recurrence is etiology and presence of neurological abnormality at baseline.[22,27] In the North London cohort, children with pre-existing neurological abnormality were 3.8 times (95% CI 1.8–8.0) more likely to have a CSE recurrence during follow-up. In addition, compared to children who presented with CSE as first episode, children who had already had previous CSE at baseline were 4.5 times (95% CI 1.8–11.1) more likely to have CSE recurrence during follow-up. In the PFS group, 10 children (29%, 95% CI 16–45) had CSE recurrence, and of these, four had epilepsy diagnosis during follow-up.[27]

MOTOR AND/OR COGNITIVE DISABILITY

Children with a history of CSE have a higher prevalence of neurologic disability including focal neurologic deficits (e.g., hemiplegia, diplegia, extrapyramidal syndromes, and cerebellar syndrome). It is often difficult to determine whether reported motor and/or cognitive impairments are new or predates the CSE episode as most studies do not report them separately.[7,46] Furthermore, in most studies, cognitive outcome is determined by no formal neurocognitive testing or using global measures such as full scale intelligence quotient, which are not designed to identify specific problems such as memory impairment or dyslexia.

Overall, the risk of neurological sequelae within 5–10 years after CSE ranges between 14% and 37%, with most of the high-quality studies reporting rates of <15%.[7,14,19,27,47-54] In the North London study, new motor disability was observed in 2.1% and intellectual disability in 8.8% following CSE due to all causes.[27] At follow-up, the prevalence of motor and intellectual disability was 30.6% (95% CI 23.4–38.8) and 45.5% (95% CI 37.3–54), respectively.[27]

Etiology was the main determinant of neurological morbidity after CSE. In the North London study, no child with PFS and acute symptomatic CSE developed motor disability and one child who had PFS developed intellectual disability. Motor and intellectual disability was seen predominantly in remote symptomatic CSE and idiopathic and cryptogenic CSE group.[27] Data from the same cohort showed that children classified as non-PFS at baseline have a worse cognitive outcome associated with the presence of cognitive delay pre-CSE, whereas there were no long-term memory impairments in children with a history of PFS.[55] In another retrospective hospital-based study, about 29% of children with reportedly normal development at baseline had developmental regression or significant cognitive impairment at follow-up.[22] Similar to the results of the North London study, symptomatic etiology, developmental delay at baseline, and abnormal brain magnetic resonance imaging were associated with increased risk of abnormal neurocognitive outcome.

BEHAVIORAL IMPAIRMENTS

It is difficult to determine the impact of childhood CSE on behavioral impairment and psychiatric morbidity separate from other neurological outcomes as it is often not reported in most studies and where reported it is uncertain whether they are new or precede CSE episode, and also if these are due to the underlying etiology of the CSE or a consequence of the CSE itself. The population-based North London CSE in childhood study examined the long-term behavioral and psychiatric outcomes using standardized questionnaires and neuropsychiatric assessments in a cohort of 134 children with CSE.[56] After a mean follow-up of 8 years, 37% had behavioral

problems and 28% had a psychiatric disorder. Fifteen of these (11.2% of total CSE cohort) were either newly diagnosed, had an additional diagnosis or revision of their diagnosis, which indicate that children with behavioral difficulties may go undetected by caregivers and the professionals. Seizures before CSE and recurrent CSE increased the risk of adverse behavioral outcomes. Of note, 8 (21.6%) children who had a psychiatric diagnosis did not have epilepsy, and hence, their behavioral difficulties cannot be attributed to ongoing epilepsy and/or the use of antiepileptic medications. These data indicate that children with CSE in childhood may often have behavioral and psychiatric impairments several years after the episode and hence require screening.

QUALITY OF LIFE

Health-related quality of life (HRQoL) is very important outcome measure that determines the quality of an individual's well-being by looking at multidimensional aspects of a person's life such as physical and social function, behavior, cognition, and emotional well-being, which are difficult to quantify.[57] Despite considerable morbidity in this population, there are very few studies addressing quality of life in children with CSE.

A population-based long-term prospective study of adults with childhood-onset epilepsy demonstrated no significant difference between those who had experienced CSE in childhood and those who did not in relation to educational attainment and employment, marital, and socioeconomic status.[43] In contrast, a more recent cohort study of children with newly diagnosed epilepsy reported that children with CSE have significantly poorer HRQoL as compared to children who did not have CSE and that this factor is independent of other factors (demographics or clinical features) which are known to affect HRQoL in childhood epilepsy.[8] However, follow-up of this cohort showed that the short-term poorer HRQoL may resolve over long term with similar HRQoL for children with and without CSE at 10 years follow-up.[58]

PREDICTORS OF LONG-TERM PROGNOSIS AFTER CHILDHOOD CSE

It is now clearly established that etiology is the most important predictor of long-term mortality and morbidity after childhood CSE.[7,19,21,27,46,55,56] In children with symptomatic causes and pre-existing neurological abnormalities, there are increased mortality and higher incidence of neurological sequelae, whereas in previously neurologically normal children, the incidence is low. The additional effect of CSE characteristics such as younger age at CSE, focal seizure onset, and seizure duration on subsequent outcomes is uncertain due to the inherent difficulty in separating the effect of CSE itself from its cause.

CONCLUSION

The data from long-term follow-up studies, albeit limited, are reassuring and suggest that the long-term prognosis is favorable in previously normal children after childhood CSE. While there are considerable mortality and morbidity associated with childhood CSE, it is mainly seen in children with symptomatic causes and pre-existing neurological impairments. Recurrence of CSE is predominantly seen in children with previous neurological abnormalities. Etiology is the primary determinant of outcome, while the role of CSE characteristics such as seizure duration seems less than previously believed. With the change in the definition of CSE, future studies investigating outcomes in children with prolonged seizures (>5 min) may help determine whether earlier cessation of seizures (<30 min) may result in better outcomes.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Electroencephalogram and pitfalls in children: Benign variants and how they can be misinterpreted

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ABSTRACT

Electroencephalogram (EEG) has been a useful tool in the diagnosis of epileptic and non-epileptic findings for about 100 years now. The interpretation of this test requires added training for neurologists in epilepsy and EEG reading. There are many findings that may be misread or overcalled as abnormal when the findings are actually normal variants in specific age groups. A misdiagnosis may result in unnecessary medications or other treatments that can potentially result in morbidity and even mortality, the latter being seen in incorrect diagnosis of status epilepticus leading to aggressive therapies. Available history and careful analysis of the EEG used together at the time of interpretation can avoid these sources of morbidity and mortality as well as a misdiagnosis of epilepsy.

Keywords: Pediatric EEG, EEG misinterpretation, Benign variants

INTRODUCTION

Electroencephalography (EEG) was first described by Hans Berger in 1929. Since that first description, EEG has been widely used to aid the clinician in an accurate diagnosis and management of epilepsies. While the EEG is an extremely useful tool in diagnosing epilepsy, this test should be used in conjunction with the available clinical history and any imaging studies and not as a diagnostic tool by itself.

The interpretation of the EEG should be done in a step wise and organized fashion to avoid over calling, or even under calling the findings while keeping in mind that the interpretation depends heavily on the training and the comfort level of the reader.

Understanding of normal pitfalls, variations in normal EEG and study of benign variants are important things to learn in EEG.[1] Determination of the clinical significance of focal or generalized spikes or epileptiform discharges may also be a source of confusion and a potential pitfall.[2] Therefore, a sound understanding of the EEG as a whole – one that includes normal age-specific findings, normal variants and abnormal epileptiform and non-epileptiform discharges are needed for an accurate diagnosis.

Pediatric EEGs differ from adult EEGs in many aspects. Interpretation of neonatal EEGs specifically require special emphasis and time during fellowship training. Therefore, ideally pediatric and neonatal EEGs should be read by a pediatric neurologist with additional training in epilepsy and neurophysiology.

INTERPRETATION OF THE EEG

Interpretation starts with an understanding of normal findings for different age groups in children. The neonates, for example, have very specific findings that evolve from week to week as the child grows. This is in contrast to an older child whose EEG may not change significantly as the child grows with a few minor exceptions. This is in addition to an understanding of age-specific physiologic and non-physiologic artifacts and variants that may not represent brain pathology. As the reader becomes more comfortable with accurate recognition of the normal EEG and its variants, then a study of the abnormal EEG should be undertaken.

AWAKE EEG

Recognition of a normal awake record starts with ensuring a correct montage, sensitivity, and filter settings. This is followed by confirming the presence of the awake state by noting the presence of eye movements, eye blinks, muscle artifact, and the presence of a posterior dominant rhythm in the correct range depending on the age of the child. Slight variations between the right and the left side in the amplitude of the posterior dominant rhythm may be seen and often fall within the normal range of acceptable variability. The reactivity of the posterior dominant rhythm to eye opening or closure clearly distinguishes this rhythm from any possible pathological rhythms. Posterior dominant rhythm that is reactive to eye opening appears between 3 and 4 months of age in about 75% of full-term infants.[3]

The response of the normal brain to activating procedures such as hyperventilation and photic stimulation should also be carefully analyzed as these may sometimes be confused with abnormal brain activity.

NORMAL VARIANTS IN AWAKE EEG

In addition to findings seen consistently in all the patients such as eye blinks and posterior dominant rhythm, there are other findings or variants that may be seen in certain circumstances or in a small group of patients. Understanding the nature, location, morphology, and setting of the variants is essential to not confuse them with abnormal discharges or as abnormal findings.

A common occurrence, especially in active children with difficult set ups, is an inaccurate electrode placement, such that the distances between the electrodes are either too short or too large. This may misguide the interpreter to believe that there is an asymmetry of voltage when in fact the electrode placement is inaccurate.

Mild voltage asymmetries in the posterior dominant rhythm between the right and the left hemispheres are common and should not be overcalled. In almost all the children, an asymmetry between the two hemispheres of about 20% may be seen with lower voltage seen on the left side.[3]

Mu rhythm is a normal rhythm in the alpha range located in the central regions. Only about 5% of children under the age of 4 years would have a clearly defined mu rhythm. The incidence then increases with age until it reaches 18% by 16 years of age. This rhythm is usually seen more often in girls than boys.[4,5] This rhythm has an arch like morphology [Figure 1] and does not block with eye opening, but does block with movement of the contralateral extremity.

Mu rhythm is usually seen only on one side at a time and the voltage is prominent and higher than the rest of the EEG.[6] This rhythm is not consistently seen and may be easily confused with asymmetry, especially due to a skull defect as may be seen with bur hole or with prior history of brain surgery. This abnormal asymmetry would be a continuous finding and may be associated with underlying slowing, while mu rhythm would not be associated with underlying slowing and is not continuous [Figure 2].

Lambda waves may be recorded bilaterally in the occipital regions in a child who is alert and awake with eyes open and likely scanning a book or a complex picture. They are surface positive, however in a child, these waves could have a sharp component that is surface negative. They may be asymmetrically present only on one side.[3] The presence of these waves only on one side can lead the interpreter to believe the waveforms to be pathologic spikes. Young children can have benign focal epilepsies of childhood originating in the occipital regions, and one is certainly prone to mistakenly identify this normal variant as an abnormal finding. One can differentiate between the two by asking the child to close their eyes. Lambda waves would disappear with eye closure, while occipital spikes would persist [Figures 3 and 4].

Hyperventilation, an "activation procedure" is a standard part of any routine or long-term EEG in a cooperative patient. The patient is asked to hyperventilate for 3–5 min and response on the EEG is noted. Most common response seen in children is a gradual buildup of delta frequencies with voltages reaching up to 300 microvolts. This activity may be more prominent in the occipital regions and may persist for about a minute or so after cessation of the activation procedure. More robust responses are seen in children between the ages of 8 and 12 years.[3,7] This high voltage, paroxysmal rhythmic activity may sometimes be confused with sharp waves or encephalopathy. While 3 Hz spike-and-wave discharges may be seen in children with absence epilepsy, the organization and abrupt onset and offset of the spike-and-wave complexes make it easier to differentiate from physiologic hyperventilation activity.

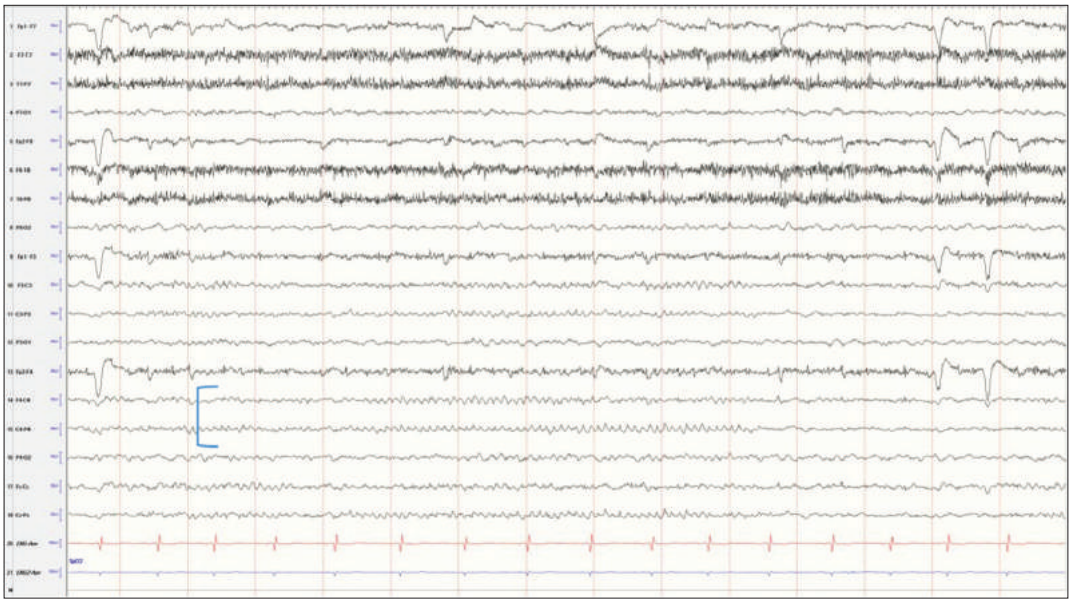

Figure 1: Mu rhythm in a developmentally normal 9-year female.

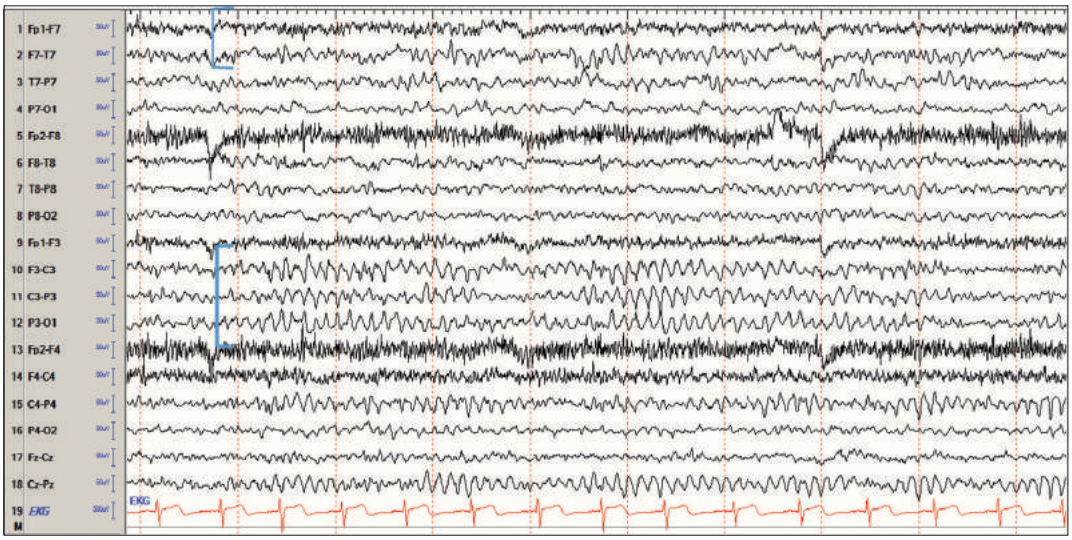

Figure 2: Asymmetry due to skull defect (breach rhythm) in the left central region in an 11-year-old girl with a history of epilepsy surgery. Note the slowing in the left temporal chains indicating cortical dysfunction – in this case, the resection.

SLEEP EEG

Sleep EEG findings start when the child shuts their eyes clinically with corresponding changes in the EEG that includes fragmentation or disappearance of the posterior dominant rhythm, and overall slowing of the EEG with a loss of the anterior to posterior gradient. There is also disappearance of eye blinks and muscle artifact with an appearance of slowing roving eye movements and possible vertex waves in the drowsy state. These vertex waves become clearer as the child continues to sleep. As the child transitions to stage 2 sleep, in addition to vertex waves, sleep spindles appear in the para sagittal regions in a synchronous fashion. However, the sleep spindles may be asynchronous in a young child with incomplete myelination of the corpus callosum as would be the case in a child under the age of 2 years. Slow wave sleep is characterized by generalized diffuse slowing and rapid eye movement (REM) sleep with bursts of saccadic eye movements with a lack of eye blinks and muscle artifact.

NORMAL VARIANTS IN SLEEP EEG

The most common mistake by an interpreter not used to the pediatric EEGs is the presence of vertex waves [Figures 5 and 6]. In younger children, these waves can have a sharper appearance than older children and adults. These

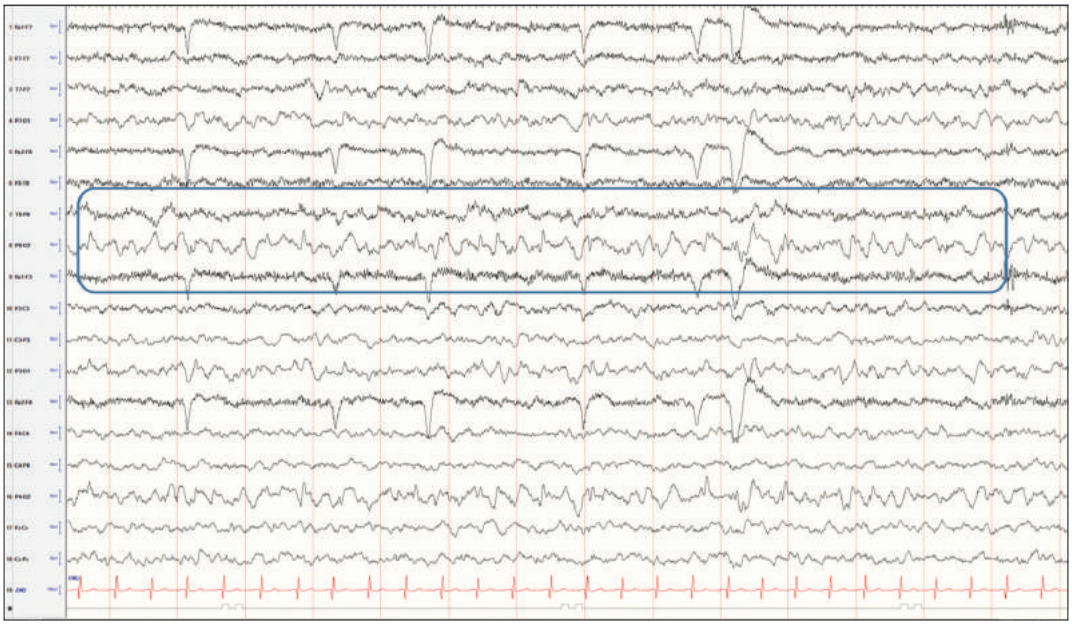

Figure 3: Posteriorly located biphasic sharp waves in an awake child scanning a complex picture consistent with lambda waves.

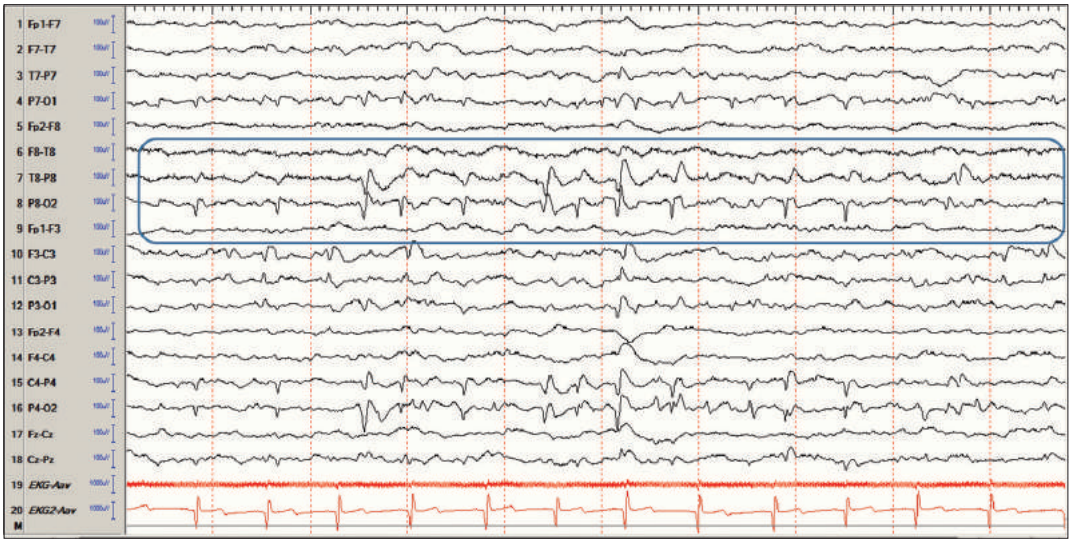

Figure 4: Occipital spikes with a prominent negative component and a field extending anteriorly in a child who is sleeping. Compare the morphology and the state of the patient with lambda waves.

can also appear in short bursts, especially as the child is in the early stages of sleep. This can understandably lead to an incorrect diagnosis of epilepsy if attention is not given to the state change, the morphology of the waves and the distribution of the waves. In terms of distribution, vertex waves would be expected to be seen predominantly in the parasagittal regions and decrease in frequency or disappear as the child drifts into stage 2 or stage 3 sleep.

It is important to note that vertex waves are a normal phenomenon related to early sleep stages and should not be confused with epilepsy arising from the vertex or the parasagittal regions. In the case of focal epilepsy, the spikes would be present in the awake state in addition to sleep, may have an after-going slow wave and persist through different sleep stages and may also be associated with focal slowing in the affected region [Figure 7]. This finding then should be taken in the context of the seizure semiology to arrive at the correct diagnosis.

A child with lambda waves in wakefulness may also display positive occipital sharp transients of sleep or POSTS. A study by Egawa *et al.* reported the highest incidence of POSTS in the first 30 min of non-REM sleep after falling asleep.[8] This

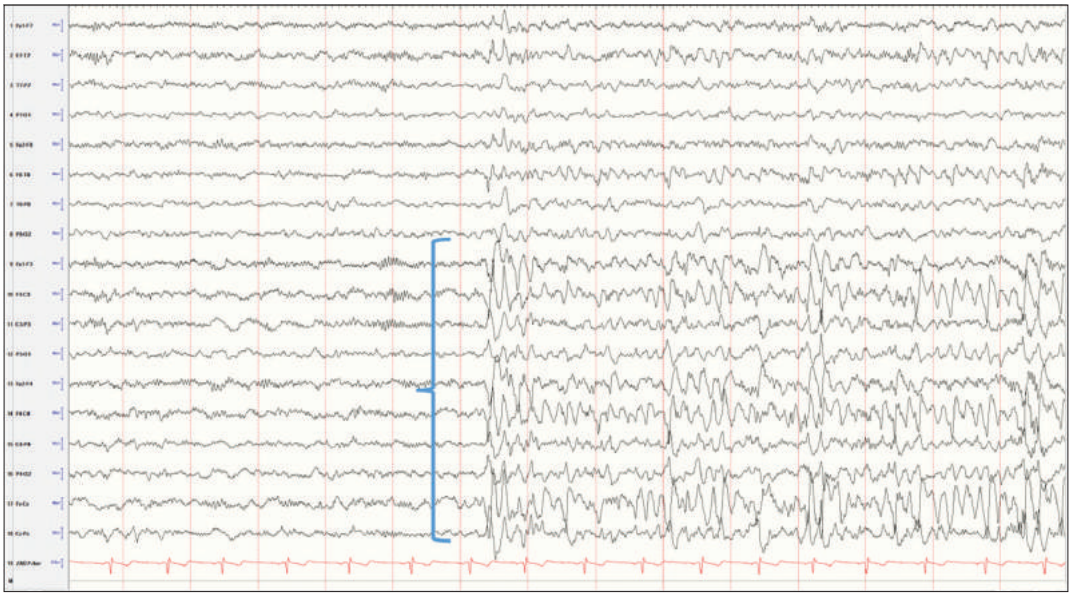

Figure 5: Vertex limited to the parasagittal electrodes in early stages of sleep in a young child.

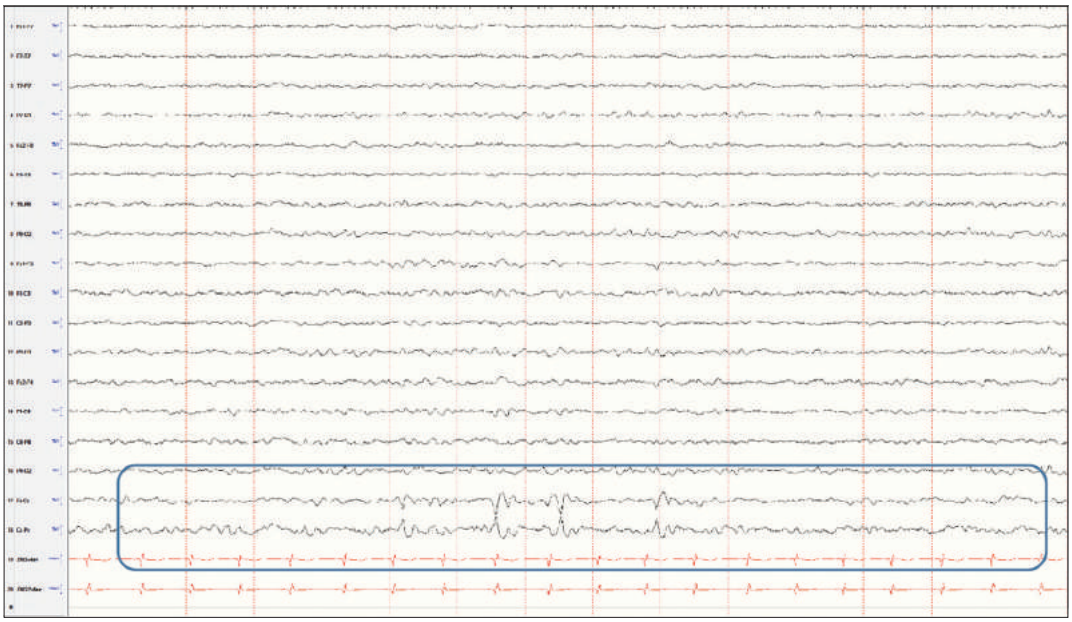

Figure 6: Vertex waves limited to the Cz electrode in sleep.

is a common finding mostly seen in older children. Again understanding the principles behind "distribution" of waveforms become essential to characterize these waveforms as normal variants rather than an abnormal finding. The main characteristic that sets these waveforms distinct from epileptiform discharges is that POSTS are surface positive, as opposed to spikes or epileptiform discharges which are surface negative. These abnormal waveforms may be present through different stages of wakefulness and sleep. A closer analysis of the morphology of the waveforms would also reveal a clear difference from epileptiform spikes, in addition to a slow wave and the absence of slowing in the background [Figure 8].

Another normal pattern that can cause confusion is the 14 Hz and 6 Hz positive bursts. These are commonly seen in drowsiness and light sleep stages. The faster frequency is more common than the slower one. These waveforms appear in short bursts lasting about 1 s in duration and have a positive "spikey" appearance and the negative wave is rounded.[3] The location of these discharges is the posterior

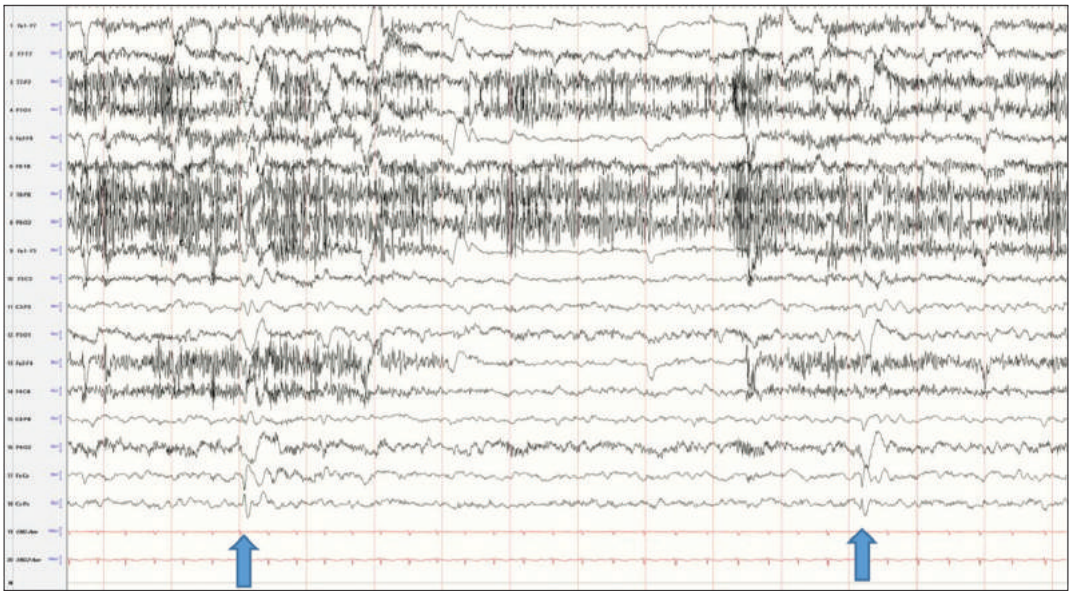

Figure 7: Spikes in the vertex electrodes, maximum in Cz (arrows). Note the difference between these waves and the vertex waves. These are present while the patient is awake, which vertex waves would not be seen in wakefulness.

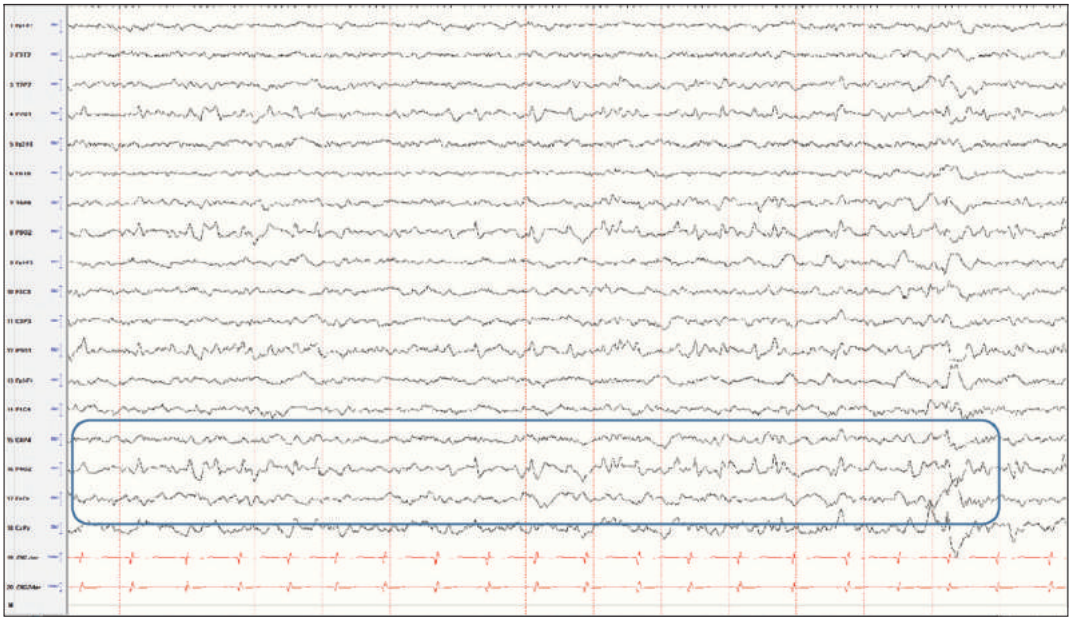

Figure 8: POSTS seen in a child with no history of epilepsy in sleep. The morphology of these waveforms resemble those of another benign variant, the lambda waves and is not to be confused with occipital spikes.

temporal region [Figure 9]. Given the spikey appearance, these waveforms may be confused with polyspikes. When analyzed closely, one would see that the spikey component is actually of positive polarity, as opposed to an epileptiform discharge which would have a negative polarity for that component of the waveform. The other clue that separates the 14 and 6 positive bursts from pathologic polyspikes is the arch-like morphology, the absence of after-going slow wave, and the absence of slowing of the background at the time of the appearance of these bursts. Another clue is the appearance only in early sleep stages and their absence in the awake state.

WHERE DOES THE INTERPRETATION GO WRONG?

The key to not over calling findings on the EEG is related to an understanding of the basis of a seizure and

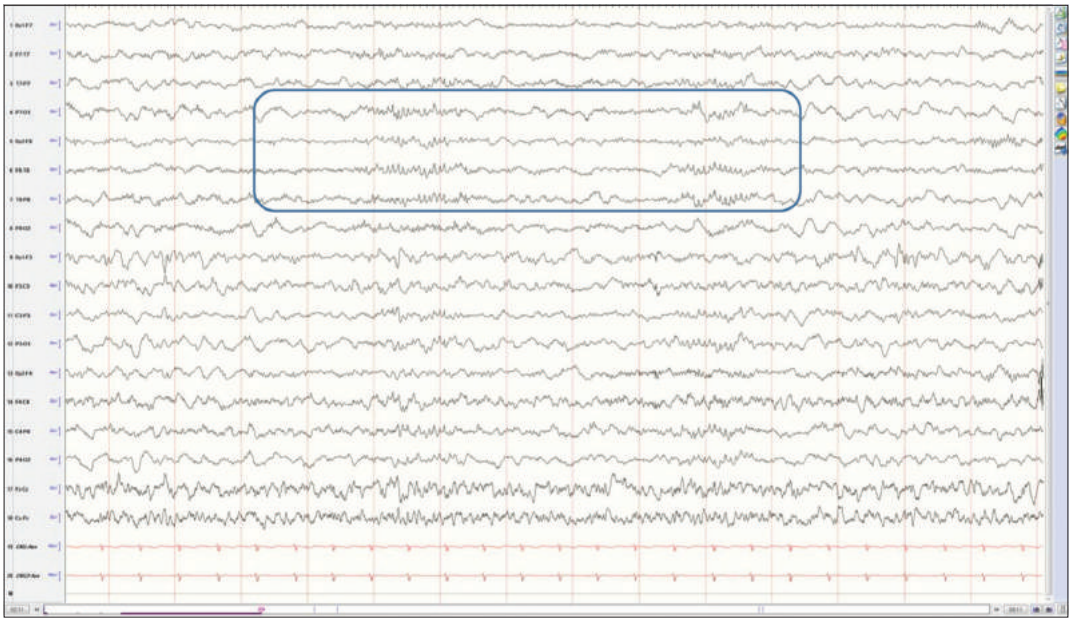

Figure 9: Fourteen and six positive bursts in an 8-year-old boy in light sleep stages. The bursts are seen in both hemispheres and last about 1 s in duration.

interictal epileptiform discharges. This is in addition to an understanding of the maturation of the brain for a pediatric neurologist/epileptologist. The former applies to a pediatric reader and the latter to someone who is interpreting neonatal EEGs. Another important aspect is to understand the "art" of analyzing a waveform in depth rather than simple pattern recognition. The analysis would help with understanding the true polarity of the waveform, or a segment of a waveform (the spikey component), and will help in determining the field of the waveform in question. Another aspect to remember is that normal variants would have a broader field on the EEG than epileptiform discharges, and shifting lateralization between the left and the right sides.[9]

Once the analysis has been completed, the reader then should be able to conclude what the true nature of a waveform truly is.

CONCLUSION

An EEG is an extremely useful tool in the diagnosis of seizures and even specific epileptic syndromes. However, its utility is a lot broader than just epilepsy and helps greatly in the diagnosis of non-epileptic events, delineation of the degree of encephalopathy, and plays a role in assisting the clinician in the prognosis.

The interpretation of this test greatly depends on the reader. The interpretation is especially challenging in the pediatric patients given the vast majority of variants seen in this age group as well as the artifacts related to movement in young children. A correct interpretation, therefore, requires the reader to have experience in reading pediatric EEGs and to be comfortable with recognition of normal variants and be able to separate these from pathologic findings. When in doubt, the electroencephalographer should look at the bigger picture and incorporate clinical history, imaging studies, and a careful analysis of the findings in question.[10] Benbadis and Tatum in their paper reported that most of the overcalled patterns happened to be normal fluctuations of the background.[11] Overcalling the findings may result in unnecessary medication use and wrong diagnoses.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Review Article

Magnetic resonance imaging brain sequences in pediatrics

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ABSTRACT

There are various pediatric magnetic resonance imaging (MRI) protocols followed in institutes and by individual radiologists, determined by the disease process and the indication for imaging, to narrow down the differential diagnosis. Most times, it is beneficial to modify protocols when the scans are being done, based on the findings seen on initially acquired sequences. This is particularly useful in pediatric patients considering most of them are scanned either under sedation or general anesthesia, and repeat scans will be cumbersome. In this particular review article, we are going to discuss appropriate MRI sequences in scanning pediatric brains and the need for rapid MRI sequences. This is of immense importance as MRI in pediatric patients poses challenges both to radiologists and technologists. Consequently, appropriate MRI protocols should be set to avoid repeat studies.

Keywords: Magnetic resonance imaging, Protocols, Rapid sequences, Pediatric, Brain

INTRODUCTION

Magnetic resonance imaging (MRI) brain sequences in pediatrics should be standardized in such a way that the scans are done in minimum time, have great image quality without artefacts, and sufficient enough to arrive at the diagnosis. The use of advanced imaging techniques such as perfusion, tensor imaging, or spectroscopy is rarely required. Although most of the protocols can be designed as per the clinical indication and age of the patient, scans should be monitored by the radiologist, and the need to modify sequences or use IV contrast be justified. The technologists should be trained to apply particular protocols in children and be confident enough to modify even when the radiologist is not around. The technologists must be well aware of rapid MRI protocols which are particularly useful in patients less than 2 years of age.

CHALLENGES ENCOUNTERED IN SCANNING PEDIATRIC BRAINS

The major challenge is to keep the children still through the scan duration. This can be done either by intravenous sedation, general anesthesia, or oral sedation. Older children usually are more co-operative, but the younger ones require some sort of intervention. Apart from sedation, premature infants pose further challenges as there is a need for maintaining body temperature and safe transport. A trained nurse or neonatologist should accompany the neonate to monitor the homeostasis during the scans. Even MR compatible incubators can be used for transport and during the scan without degrading the image quality.[1] Not so sick infants usually sleep after feed and rarely require sedation. Sedation should be given by a trained nurse, who should also be

responsible for the child till recovery and help in obtaining good image quality without motion artefact.[2] Most institutes or hospitals, including ours, prefer anesthetists or pediatricians to administer sedation or general anesthesia. All sedated infants and children should be monitored for cardiorespiratory parameters throughout the scan until recovery. Furthermore, care should be taken to keep the children warm and use earplugs or earmuffs to avoid movement.[3] Older children between 2 and 5 years can be given oral sedatives such as chloral hydrate or Phenergan for completing the scans. Sometimes, intravenous sedation like propofol with an infusion dose of 2–5 mg/kg/h can be used with short induction and early recovery. Other intravenous drugs which are used for sedation are dexmedetomidine (loading dose 2–3 μg/kg and maintenance infusion 1–2 μg/kg) and pentobarbital.[4-6]

Almost all institutes or hospitals have adult MRI coils, while very few pediatric institutes have dedicated pediatric coils, which have an obvious advantage in terms of image quality compared to adult coils. However, it is always preferred to use high filed magnets like 3 Tesla MRI with dedicated multichannel phased array coil, fast imaging sequences, parallel imaging, compressed sensing to reduce scan time and improve the image quality.[7,8]

Whatever coils used, pediatric brain imaging should be done with a slice thickness of 5 mm for brain and 3 mm for orbit and pituitary scans. Some authors prefer to use advanced multichannel head and spine coils for pediatric imaging and avoid ultrafast breath-hold T2W imaging with low signal to noise ratio for obvious reasons.[9]

USE OF CONTRAST IN PEDIATRIC BRAIN IMAGING

As in adults, all precautions should be taken before the administration of intravenous MRI contrast for safety purposes. Prior renal function tests should be done. In the majority of the cases, contrast is seldom required. The common indications for contrast in pediatric brains include infection, demyelination, tumors, metastases, CSF and cranial nerve pathologies, neurocutaneous syndromes, and vascular pathologies. Sometimes, contrast is used to perform specific functional scans like perfusion-weighted imaging or contrast-enhanced angiography, depending on the clinical need. The advantages of contrast imaging include detecting, localizing, and characterizing the lesions and in follow-up imaging, especially post-treatment tumors and demyelinating diseases.[10]

Various gadolinium-based MRI contrast is available such as gadodiamide, gadopentetate dimeglumine, and gadobenate dimeglumine which have a linear polyaminocarboxylic acid structure that incompletely encircles gadolinium ions, whereas macrocyclic agents such as gadobutrol, gadoterate meglumine, and gadoteridol completely encircle the gadolinium ions thus making them more stable and safe especially in terms of developing nephrogenic systemic fibrosis.[11-14]

Dosage is weight dependent just as in adults (0.1 mmol/kg body weight) and is not based on age. This is proved even in pediatric patients below 2 years with gadobutrol.[15] Most of the contrast agents are in 0.5 molar concentration except gadobutrol which has 1 molar concentration. In general, gadobutrol is considered a safe and efficient MRI contrast agent in children.[10]

STANDARD MRI BRAIN SEQUENCES

MRI has specific advantages over other modalities such as computed tomography – no ionizing radiation, increased tissue contrast, multiplanar multisequence capabilities, and functional imaging. Combinations of various sequences help in diagnosis and the aim is to apply the most appropriate sequence to reduce time and acquire good quality images.

SEQUENCES FOR ASSESSMENT OF MYELINATION

Pediatric brain undergoes rapid changes in the first 2 years in terms of growing myelination and reducing brain water content. Hence, it is important that proper MRI sequences are selected to differentiate pathology from normal myelination and also to look for the occurrence of age-appropriate myelination which requires good tissue contrast.[16]

Up to the first 6 months of life, T1-weighted images are useful, which show hyperintensity of myelinated fibers (dark to bright); thereafter, up until 2 years, T2-weighted images are useful where the maturing myelinated fibers appear hypointense (bright to dark). Due to poor gray matter white matter differentiation before 6 months of age, subtle subcortical lesions can be obscured, but after myelination which appears T1W bright, the subcortical pathologies can be seen on T1W images.[17] Fluid attenuation inversion recovery (FLAIR) is not particularly useful in children due to high water content.[9] Typically, FLAIR sequence shows a triphasic pattern in children. In young infants, deep cerebral white matter is heterogeneously hypointense (relative to gray matter), in early months, it becomes hyperintense and then in 2nd year of life, it again becomes hypointense. This pattern must be known to avoid misinterpretations.[18]

Similarly, due to unmyelinated fibers and high water content, diffusion-weighted images are also not very useful in the early period of life. It shows a significant reduction in ADC with advancing age.[19]

Dual-echo short-tau inversion recovery (STIR) sequence is also useful below 2 years which shows increased contrast resolution (TE 30/128 ms, TR 5,400 ms, and TI 130 ms).[9,20]

Instead of T1W sequence, 3D gradient-echo T1-weighted pulse sequence like magnetization prepared rapid gradient echo (MP-RAGE) can be used.

In summary, to detect age-appropriate myelination, spin-echo (SE) T1W or 3D MP-RAGE, T2W, and STIR axial sequences can be used.

ROUTINE BRAIN SEQUENCES

In some dedicated pediatric institutes, axial T2W fast spin-echo (FSE) and coronal FLAIR, sagittal and coronal T1W SE, DWI, and T2* gradient sequence like susceptibility-weighted imaging (SWI) is used in children more than 2 years. In addition, in children below 2 years, dual-echo STIR axial and coronal is used instead of T2W FSE. SWI sequence specifically is added to assess any blood products. If contrast is given, then coronal/axial SE T1W with magnetization transfer (MT) are added. In neonates, slice thickness can be reduced to 4 mm, matrix size and FOV can be reduced, and adult knee coil can be used to improve the image quality.[9]

In our practice, we follow 3D FLAIR, 3D MP-RAGE, DWI/T2W/SWI axial, and T2W coronal sequences. Inclusion of these help assesses midline structures like corpus callosum and brainstem and anterior structures like optic nerves and optic pathway, para cavernous, and orbital/paranasal sinuses. 3D sequences are more useful to assess periventricular structures and anterior-most middle cranial fossa lesions. If contrast is given, then post-contrast 3D T1 MP-RAGE and axial T1W with MT are used.

BRAIN SEQUENCES IN VARIOUS DISEASES

Orbit, inner ear, and pituitary lesions

To assess orbital lesions, including optic nerves and optic pathway and the pituitary, dual-echo STIR and T1W SE fat-saturated (FS) sequence in coronal and axial planes are used to suppress orbital fat with a slice thickness of 3 mm and small matrix size to increase tissue contrast. If contrast is given, then FS T1W axial and coronal is used. For pituitary lesions, sagittal and coronal T1W and coronal T2W with additional T1W coronal and sagittal post-contrast are used. For inner ear structures, including internal auditory canal, heavily T2W sequences such as CISS 3D (SIEMENS), FIESTA in GE, and DRIVE in Philips are used apart from the standard.[9]

We use thin 3 mm slice thickness, axial and coronal STIR or FS T2W, and sometimes oblique sagittal in plane with optic nerves to assess orbit and optic nerves. If contrast is used, then FS T1W axial and coronal are added. Same sequences can be used to assess paranasal sinuses and the pituitary gland with the addition of FS T1W sagittal. Dynamic contrast study in coronal planes for the pituitary gland can be used if indicated. Post-contrast T1 MP-RAGE has not been found useful to assess contrast enhancement in the pituitary gland or orbit due to air (of paranasal sinuses) tissue interface artefacts.

Brain tumors

For characterization of brain tumors in terms of location, size, multiplicity, spread, and complication like hydrocephalus, standard brain sequences with contrast as described above are used. In addition, all children with brain tumors should have their spine imaged, preferably with contrast T1W FS sequence, to detect distant metastases.[21] It is wise to use a volumetric 3D sequence such as pre-contrast FLAIR or post-contrast T1W (MP-RAGE) without using ear muffs for neuronavigation guided surgery.

Advanced imaging techniques such as MR contrast enhanced dynamic perfusion (DSC), arterial spin labeling perfusion (ASL), MR spectroscopy, and diffusion tensor imaging are usually used to characterize tumor type but rarely required in children. However, these advanced imaging techniques are useful in post-operative children who have received radiation to differentiate between tumor recurrence and radiation necrosis. In children, ASL perfusion study can be useful which does not require contrast.[22]

Immediate post-operative MRI scans within 72 h are usually performed with contrast to avoid interference of post-operative changes such as edema and blood products with tumor residue.[21] Sometimes intra-operative MRI scans are done to assess tumor residue, preferably with contrast. It is important to find pre-operative image characteristics of tumors while doing intra-operative scans to use appropriate sequences which can highlight the residual tumor.

Follow-up MRI brain scans in treatment received brain tumors should include imaging of the spine even if there is no residual tumor since early detection of spinal metastases helps improve overall survival.[23,24]

We prefer to add post-contrast FLAIR axial for brain and FS T1W sagittal sequence for spinal imaging to detect distant metastases. Post-contrast FLAIR is found to be more useful to detect leptomeningeal metastases.[25]

Infections

Standard imaging protocols should be used along with contrast to characterize the type of lesions. Usually, in meningitis and meningoencephalitis, addition of post-contrast FLAIR along with T1W MT sequence yields better visualization of meningeal enhancement.[26] In our practice, both post-contrast FLAIR and T1W with MT are found useful; however, 3D T1 MP RAGE sequence is not found to be adequate to evaluate meningeal enhancement

[Figure 1]. Sometimes it is useful to find the source of infection such as mastoiditis or sinusitis and add additional sequences accordingly. Screening of spine with post-contrast T1W sagittal FS sequence will show any changes of spinal meningitis.

In cases of ring-enhancing lesions, the addition of heavily T2W sequence, DWI, SWI, MR spectroscopy, or perfusion will help to accurately arrive at the diagnosis. These advanced imaging sequences will help differentiate between metastatic ring lesion, abscess, tuberculoma, or neurocysticercosis. CISS sequence is useful to detect scolex in cysticercosis, SWI is useful to detect calcification in granulomatous disease and detect hemorrhage in hemorrhagic meningoencephalitis, DWI is useful to detect pyogenic abscess and spectroscopy and perfusion to differentiate neoplastic from non-neoplastic lesions.[27-30]

Hydrocephalus

Hydrocephalus can be communicating or obstructive. In addition to routine imaging protocol, 3D T2W SPACE/heavily T2W sequences such as CISS 3D and SWI should be added. 3D T2W SPACE and heavily T2W sequences help identify the type. SWI sequence helps to identify any blood products or previous hemorrhage as a cause of communicating hydrocephalus.[31] Contrast MRI can be useful to detect the infective cause of communicating hydrocephalus.

CSF flow study can add value in detecting the cause of hydrocephalus. It can be done across the aqueduct or foramen magnum in case of Chiari malformation. It is also useful to detect flow patterns in intracranial arachnoid cysts and in shunt malfunction.[32]

Metabolic disease and leukodystrophy

In evaluating children with leukodystrophy, majority of the time, standard brain protocol is sufficient. In addition, spine screening with T2W sagittal can be done to assess spinal cord involvement and MR spectroscopy to detect metabolite abnormalities. MR spectroscopy can show pathognomonic findings in a few leukodystrophies like Canavan disease and metabolic diseases like mitochondrial cytopathies.[33]

Demyelinating diseases

In addition to routine standard imaging protocols, imaging of orbits and spinal screening should be performed, preferably with contrast. Orbital coronal STIR is used to detect optic neuritis and enhancement on coronal FS T1W. Spinal screening can be done with T2W sagittal and post-contrast T1W FS sagittal to detect spinal lesions and their enhancement. Post-contrast FLAIR will be useful especially to detect periventricular lesions and their enhancement. 3D FLAIR or sagittal FLAIR adds value to detect corpus callosal lesions. Similar protocols should be followed in follow-up scans for studying the comparative images.[34]

Epilepsy

Imaging protocols in children with epilepsy differ from routine imaging protocol. A few centers use axial T2W fast spin-echo, 3D T1W volume acquisition reconstructed in three planes, coronal T2W fast spin-echo, coronal FLAIR (or 3D FLAIR), and hippocampal T2-relaxometry. In children less than 2 years, coronal T2W is replaced by dual-echo STIR sequence. The coronal sequences are used with planes perpendicular to hippocampus.[9] T2 relaxometry is rarely used today, but it is useful to obtain T2 values in cases of mesial temporal sclerosis, especially if it is bilateral.[35]

In our institute, we use 3D FLAIR, 3D MP-RAGE T1W, 3D TSE single slab SPACE, DWI axial, FLAIR axial parallel to hippocampus, coronal dual-echo STIR or T1W IR, and T2W coronal perpendicular to hippocampus with 3 mm slice thickness and SWI. With the use of these sequences, most of the migrational anomalies, temporal and extratemporal lesions, and calcifications/hemorrhagic lesions can be detected. We recommend use of 3D T2W SPACE sequence which is a single slab 3D T2W image (PHILIPS) with the ability to reconstruct in all three planes without degrading image quality.

In some children with refractory epilepsy and normal MRI in the first 2 years of life, a second scan after brain maturation

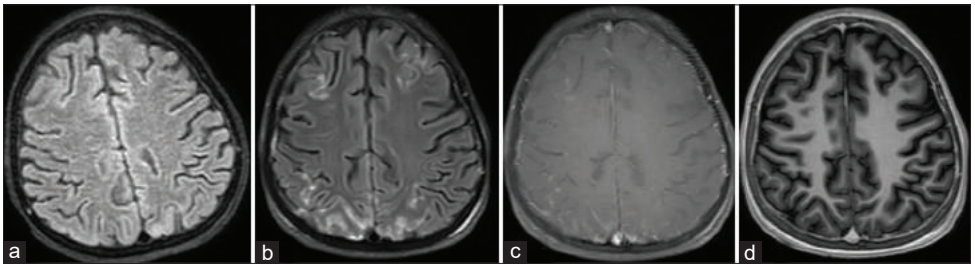

Figure 1: (a) Non-contrast fluid attenuation inversion recovery (FLAIR), (b) post-contrast FLAIR, (c) post-contrast T1W with magnetization transfer (MT), (d) axial reconstruction of 3D T1 magnetization prepared rapid gradient echo (MP-RAGE). In this case of meningitis, meningeal enhancement is clearly visible on post-contrast FLAIR and T1 with MT and not seen in T1 MP-RAGE.

Table 1: Recommended disease wise MRI protocols.

Indications	MRI protocol
Myelination	SE T1W axial/sagittal Or 3D T1 MP-RAGE SE T2W axial/coronal Or dual-echo STIR axial/coronal FLAIR axial or 3D FLAIR
Routine brain	FLAIR axial or 3D FLAIR 3D T1 MP-RAGE or T1W SE axial/sagittal DWI axial SE/FSE T2W axial/coronal Or dual-echo STIR axial/coronal SWI axial Post-contrast 3D T1 MP-RAGE T1W axial with MT Or T1W axial/sagittal/coronal
Orbit (thin slice 3 mm)	Dual-echo STIR or T2W FS axial/coronal/sagittal obliques T1W FS Coronal/axial Post-contrast T1W FS axial/coronal
Pituitary (thin slice 3 mm)	Dual-echo STIR or T2W coronal/sagittal T1W sagittal/coronal Post-contrast T1W sagittal/coronal
Inner ear	Heavily T2W sequence like CISS 3D or FIESTA or T2 DRIVE
Tumor	Routine brain sequences with contrast FS SE T1W sagittal of whole spine MR spectroscopy Perfusion
Infection	Routine brain sequences with contrast Post-contrast FLAIR axial Post-contrast T1W with MT Heavily T2W sequence like CISS 3D MR spectroscopy MR perfusion
Hydrocephalus	Routine brain sequences 3D T2 SPACE Heavily T2W sequences like CISS 3D CSF flow study
Metabolic disease/leukodystrophy	Routine brain sequences T2 sagittal spine MR spectroscopy
Epilepsy	3D FLAIR or FLAIR axial/coronal 3D T1W MP-RAGE or T1 sagittal/axial/ coronal 3D T2W SPACE or T2W/STIR/IR T1W axial/coronal DWI axial SWI axial
Demyelination	Routine brain sequences Orbital sequences FLAIR sagittal T2W sagittal spine Post-contrast axial 3D FLAIR or FLAIR axial/sagittal, T1W axial with MT, and T1W FS sagittal spine and coronal for orbits
Non-traumatic brain hemorrhage	Routine brain sequences MR angiogram MR venogram SWI axial

(Contd...)

Table 1: *(Continued)*

Indications	MRI protocol
Stroke	Routine brain sequences MR angiogram of neck and brain Dual-echo STIR and FS T1W axial of neck
Non-accidental head trauma	Routine brain sequences with SWI T2 sagittal cervical spine
Global developmental delay	Axial FSE T1W, T2W, PD FLAIR DWI IR T2W Sagittal FSE T1W Coronal IR T1W, T2W FSE, FLAIR Or 3D MPRAGE/3D FLAIR Additional sequences depending upon the initial findings

FS: Fat saturated, MT: Magnetization transfer, IR: Inversion recovery, SWI: Susceptibility weighted imaging, STIR: Short tau inversion recovery, SE: Spin echo, FSE: Fast spin echo, MP-RAGE: Magnetization prepared rapid gradient echo, CISS: Constructive interference in steady-state, PD: Proton density

(at least 6 months apart) to detect the focus of epilepsy is required.[36]

The use of 3 tesla MRI is more useful in detecting the focal epileptogenic lesions as compared to 1.5T MRI due to better image uniformity, signal to noise ratio, and spatial resolution.[37,38]

Functional MRI is specifically useful in the presurgical evaluation of the sensorimotor cortex or language lateralization. Ictal/interictal PET or SPECT are additional modalities to detect seizure focus apart from MR spectroscopy, magnetoencephalography, MT imaging, and diffusion tensor imaging.[39]

Children presenting with non-traumatic brain hemorrhage

Apart from standard imaging protocol, 3D time of flight (TOF) MR angiography, 2D or 3D phase-contrast MR venogram, and contrast can be used in non-traumatic brain hemorrhage. Sometimes if the child is not stable, CT angiography can be performed. MRI with MR angiogram or venogram should be performed after 72 h of ictus to avoid signal interference from hemorrhage. Contrast sequences are useful to detect any underlying tumor or vascular malformation such as cavernoma or small arteriovenous malformation.[9,40] We additionally add SWI sequence to detect any previous petechial hemorrhages, which could support the diagnosis of vasculitis or multiple cavernomas.

FAST/ultrafast MRI sequences can be used in unstable patients such as FAST FLAIR, EPI FLAIR, EPI DWI, single-shot FSE T2W/T1W by use of parallel imaging technique or susceptibility-weighted angiography, and HASTE sequence in coronal or axial planes, which reduce the scan time significantly and avoid the need for CT scan.[41-43]

Children presenting with stroke

The most important causes of stroke in children are cardiac, hematologic, oncologic, infective, vasculopathy/vasculitis, trauma, or drug-induced vasculopathy.[44] The imaging protocols should be set to detect any of these causes. 3D TOF MR angiography along with DWI and SWI should be done. In 80% of stroke cases, abnormalities are found in the intracerebral arteries, so doing MR angiography is very important.[45] Extracranial MR angiography with axial dual-echo STIR and FAT SAT T1W sequences of the neck will help detect arterial dissection of neck vessels and also identify vascular wall hemorrhage, especially in case of trauma.[46] Rapid and ultrafast MRI sequences can be additionally used to fast screen the suspected stroke patients where stroke mimics can be identified by FLAIR sequence.[47]

Children with non-accidental brain trauma

Although CT scan is the preferred modality in non-accidental brain trauma, MRI is done usually after 3–4 days to detect hypoxic brain injury by DWI (which is better than CT), thin subdural hematoma, or multiple petechial subcortical hemorrhages by adding gradient SWI sequences and also FLAIR. Sagittal T2W imaging of the cervical spine is also recommended to evaluate brainstem or cord injury which could be the result of violent shaking, in turn causing hypoxic injury.[48-50]

Children presenting with global developmental delay (GDD)/intellectual disability

Pediatric neurologist very often comes across children presenting with GDD. The first investigation offered is MRI. This is because MRI is found abnormal in almost 54.7% of

cases with common structural abnormality seen in white matter, corpus callosum, and ventricles. In 39.6% of cases, MRI is helpful in clinching the right diagnosis either directly or indirectly which can be confirmed by other investigations. The protocols used are Axial DWI, TSE T1W, TSE T2W, FLAIR, PD, T2TIRM, coronal T1TIR, and T2 TSE and sagittal T1 TSE.[51] For initial screening, these protocols can be used but should be modified according to the findings. For example, if there is hydrocephalus or leukodystrophy, then appropriate additional sequences should be added. Thus, it is very important to look at the imaging findings during the scan to modify the protocols to avoid redo or repeat imaging.

Disease-specific recommended MRI protocols are summarized in [Table 1].

CONCLUSION

Routine conventional imaging is sufficient to arrive at the diagnosis most times; however, a few advanced imaging techniques particularly functional MRI and spectroscopy add value. Physicians should be aware of these MRI sequences and should specifically include them in the request form, depending on their clinical diagnosis. This will save time and the need for repeat studies in children.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Newborn screening: Need of the hour

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ABSTRACT

Newborn screening (NBS) is the process by which newborns are screened just after birth for disorders that can cause severe illness or death unless detected and treated early. At present, there is no national NBS program in India. Although the exact incidence in India is not known, approximately 4:1000 and 5:1000 are estimated to have hearing defects and congenital heart abnormalities, respectively, whereas the incidence of IEMs is estimated to be approximately 1:1000. This high incidence is due to high prevalence of consanguinity in our country. If undiagnosed and untreated many children develop mental retardation, learning disabilities, autism, dyslexia, behavioral abnormalities, and scholastic backwardness later in life. There is also considerable burden-financial and emotional on the parents to diagnose, treat, and manage these children. The most rational and cost-effective way of preventing such tragedies would be to have a NBS program which will detect most of the preventable or treatable, if not all IEMs and other genetic disorders. Hence, all hospitals in urban areas in India should initiate NBS at least for the common disorders: CH, CAH, and G6PD deficiency.

Keywords: Inborn errors of metabolism, Dried blood spots, Hearing screening, 2nd tier test, Newborn screening

INTRODUCTION

Newborn screening (NBS) is the process by which newborns are screened just after birth for disorders that can cause severe illness or death unless detected and treated early. The delay or lack of diagnosis of an Inborn Error of Metabolism or other conditions which can be detected at birth, for example, hypothyroidism, G6PD deficiency, etc., can lead to severe mental deterioration. NBS tests newborns for certain metabolic and other disorders so that intervention is possible before symptoms or mental and/or physical disabilities develop. It is a norm in the developed countries and is recommended to prevent morbidity and mortality. Depending on the incidence, different countries screen for disorders ranging between 5 and 50+ disorders.

NBS was introduced in early 1960s by the pioneering work of Dr. Robert Guthrie in the USA, with the discovery of bacterial inhibition assay to detect Phenylketonuria from dried blood spots.[1] As the concept of NBS was accepted as an essential preventive public health policy, newer techniques developed and soon began to include other IEMs. Since its commencement NBS has progressed with increase in the number of metabolic/genetic disorders screened, type of samples used (from invasive to non-invasive), and improvements in technology (from bacterial inhibition assays to ELISA and RIA and now to LC/MS/MS techniques). In 1990, it was proposed that MS/MS could be used to test for multiple analytes simultaneously in dried blood spots[2] and about 40 conditions are now screened from a single blood spot by LC/MS/MS in routine NBS programs.[3,4]

In India, NBS was first carried out by Dr. Appaji Rao and Dr. Radha Rama Devi. Subsequently, many small studies were carried out at various centers across India and now many private hospitals and labs have initiated their own NBS programs. Many state level NBS programs have been initiated and of note among these are the Chandigarh Program initiated in 2007 which screened for CH, CH, and G6PD;[5] Kerala State NBS program[6] and Goa state NBS Program carried out by Dr. Rohit Cariappa.[7] However, NBS as a National Health Service program is yet to be initiated in India.

WORLD HEALTH ORGANIZATION (WHO) GUIDELINES

NBS is not simply a test for diagnosing disorders but a coordinated comprehensive system consisting of other aspects such as education, follow-up of abnormal results and confirmatory testing, diagnosis, treatment, management, periodic outcome evaluation, quality assurance, and evaluation of the whole program. The WHO has issued guidelines and criteria for selecting disorders in NBS program. Wilson and Jungner in 1996 have outlined the selection criteria for disorders in NBS program. These criteria are applicable to systematic or population-based screening of any type of disease and not only to inherited disorders.

Box 1: Wilson-Jungner criteria for disease selection in NBS

1. The condition should be an important health problem
2. Natural history of the condition should be well understood
3. It should be detectable at an early age
4. Treatment at an early stage should be beneficial
5. Suitable test should be devised for early detection
6. The test should be acceptable
7. Intervals for repeating the test should be available
8. Adequate health service provision should be made for the extra clinical workload resulting from the screening
9. The risks, both physical and psychological should be less than the benefits.
10. The cost should be balanced against the benefits.

Congenital hypothyroidism (CH) is the most common preventable cause of mental retardation. The world-wide incidence is 1:2500–2800 live births. Thyroid dysgenesis is the most common cause accounting for 75–80% of all cases of CH. In India, the exact incidence of this disorder is not known, but it seems to have a much higher incidence than the rest of the world.[8-11] It not only constitutes the most common cause of preventable mental retardation but also the therapy is easily available and economically feasible to all. First NBS program for CH was started at BJ Wadia Hospital in Mumbai in 1982 using cord blood TSH and subsequently in 1984 using post-natal T4 on DBS.[12]

Ideally universal NBS at 48–72 h of life should be done for detecting CH. If screening is being done only for CH, the cord blood may also be used. Three approaches are used for screening:[13]

1. Primary TSH (backup T4): T4 is measured only if TSH is >20 mU/L
2. Primary T4 (backup TSH): TSH is measured if T4 is <6.5 ug/dL
3. Both T4 and TSH: Both measured simultaneously. More sensitive approach but is expensive.

Primary TSH screen is more sensitive and specific for diagnosis of primary CH. Abnormal value on screening (T4 <6.5 ug/dL and TSH >20 mU/L) should always be confirmed by a repeat sampling and assays done on liquid blood samples.[14] Most centers initiate treatment after drawing the blood samples for confirmatory results and decision to withhold or continue treatment is taken after obtaining venous blood report.

G6PD deficiency is the most common enzyme deficiency affecting estimated 400 million people all over the world. It is also the most common genetic disorder in India. Although the exact incidence is not known, various studies have reported an incidence ranging from 2% to 27.9% in different communities.[8,15] It is an X-linked recessive disorder presenting with hemolytic anemia and prolonged jaundice and causes significant morbidity and mortality in childhood. There are no primary interventions available for this disease and the only way to avoid adverse outcomes is to recognize it early in life and prevent exposure to agents which can trigger hemolysis. NBS helps to identify these individuals at an early age.

NBS for G6PD has been successfully implemented in countries such as the USA, Malaysia, Singapore, Taiwan, Hong Kong, Philippines, the Middle East, and Europe. In India, NBS for G6PD deficiency has long been perceived by public and pediatric health experts. Introduction of screening program will substantially decrease the hospital admissions due to acute hemolysis, thereby reducing the number of blood transfusions and dialysis needed.

Cystic fibrosis is the most lethal, autosomal recessive monogenic disorder caused due to an abnormal transport of chloride ions across the apical membrane of the epithelial cells. The sweat glands are relatively impermeable to chloride ions resulting in increased concentration of chloride in the sweat reaching the skin surface. To maintain electro neutrality, the reabsorption of sodium ions by the sweat glands is also reduced, thereby increasing the concentration of sodium in the sweat.[16] The prevalence of this disorder in India is not known, however, there have been a few studies to study the prevalence and the common mutations in the CFTR gene in the Indian population.[17-19] Although there is no intervention available for this disorder, early detection can help in reducing the cost of tedious diagnostic procedures later in life. Screening for this is done by analyzing the levels of IRT in DBS.

Congenital adrenal hyperplasia is a group of rare autosomal recessively inherited disorders of cortisol biosynthesis. The classic defect occurs in two forms as CAH with salt wasting and as simple virilizing CAH without salt wasting. The incidence of CAH varies worldwide according to ethnicity and geography. The exact incidence is not known in India. Reported incidence is 1 in 12,000 but in the Southern part of India, the disorder seems to be more prevalent giving an incidence as high as 1:2750.[8,20] The diagnosis of classic CAH can be made at birth based on ambiguous genitalia in a newborn female or during the neonatal period in both sexes based on salt wasting crisis. Elevated 17 OHP indicates a possibility of CAH. The goal of classic CAH-NBS is early detection of the severe salt wasting form, therefore, prevention of adrenal crisis or death.

Galactosemia, caused by the deficiency of the enzyme Galactose-1-phosphate uridyl transferase, has an incidence of 1:30,000–1:60,000 in western countries.[21] Not much is known about the incidence of this disease in India but it is reported to account for up to 4% of children presenting with neonatal cholestasis syndrome in India.[22] NBS for galactosemia can be done by screening either galactose or galactose-1-phosphate levels in dried blood spots. Confirmatory testing requires enzyme analysis and may be followed by mutation studies. It is very essential to diagnose this disorder early in neonatal period as if untreated it may lead to severe life threatening episodes, affecting liver. If diagnosed early, it can be simply treated by omitting galactose from diet.

Biotinidase deficiency is a rare but easily treatable disorder caused by mutations in the *BTD* gene. Biotin which is a co-factor for several carboxylases involved in branched chain amino acid metabolism and fatty acid metabolism is recycled by the enzyme biotinidase. The deficiency may cause seizures, immune system impairment, hearing loss, mental retardation, coma, and even death. Other symptoms include apnea, tachypnea, hyperventilation, skin rashes, and alopecia. Later developmental delays, speech problems, ataxia, and hearing problems may occur. Onset of this disease is around 3–6 months of age and hence if it is detected early by NBS, treatment can be started prior to onset of symptoms. Patients with late or no treatment can manifest with permanent neurologic sequelae and hearing loss. Screening for disorder is done as a part of NBS programs in many countries and is a simple colorimetric determination. All positive tests are confirmed by a quantitative assay in serum and also may be confirmed by mutation analysis.

Fatty acid oxidation defects are now being included in NBS programs worldwide. This is a group of disorders with an estimated combined incidence of 1:9,000. Benefits have been proven the most in cases of MCAD deficiency and VLCAD deficiency by NBS for FAODs. Most FAODs are identified by Tandem Mass Spectrometry (TMS or MS/MS). Furthermore, they are treated by simple avoidance of fasting in most cases, whereas metabolic decompensation can be fatal in unsuspected patients. Due to these reasons, FAODs have been included in most NBS program since the mid-1990s.[23] In 2006, the ACMG determined 5 core conditions to be included in a standardized NBS menu. These five conditions were MCAD, VLCAD, LCHAD, CTD, and CPTII.[24] The true incidence in India is not known, however, ICMR multi-centric study has suggested a high incidence of MCAD.[25]

Aminoacidopathies and organic acidemias

Tandem mass spectrometry is also being used for screening of disorders of amino acid metabolism and organic acid metabolism. More than 20 markers for diseases are analyzed in a single assay. Disorders screened by this include PKU, MSUD, tyrosinemia, homocystinuria, argininemia, methylmalonic academia, propionic academia, and isovaleric academia. Most of these disorders present with acute life threatening episodes and may leave the affected child with permanent neurological sequelae. The exact incidence of this group of disorders is not known in the Indian population; however, the ICMR study has suggested that MMA, GAI, NKH, UCDs, MSUD, and PA are the most common disorders in India.[25]

Universal hearing NBS

Congenital hearing impairment occurs in approximately 1–5 per 1000 live births and has an incidence that is twice of all other disorders amenable to NBS. In India, the incidence has been estimated to be between 1 and 8 per 1000 babies screened. Early identification and intervention provides better prognosis.[26] Without NBS the infants may develop language delay, poor social and academic performance, and behavioral issues.[27,28] Screening done by two stage screening tests: Otoacoustic emission and Automated Auditory Brainstem Response Audiometry (BERA) can pick up most of the cases with hearing loss or difficulties.

Congenital heart diseases

Congenital heart diseases account for 5–10% of all infant deaths and about 25% of CHDs are life threatening. Prenatal sonography can identify structural heart defects but sensitivity of CHD detection is only about 50% by this method as it is dependent on expertise, gestational age, fetal position, and type of the defect and may miss some patients. Sensitivity of physical examination is also approximately 50%. Addition of pule oximetry to these 2 modes can improve the chances of detecting CHDs in newborns. Screening by pulse oximetry may be beneficial as it is painless, readily available in all hospitals, and requires less training hence can be handled by anyone. This test measures the percentage of O2 saturated hemoglobin and pulse rate. Overall sensitivity

of pulse oximetry in detection of HDs was 76.5% with a specificity of 99.9%.[29]

Expanded NBS

With the introduction of MS/MS, an accurate and cost-effective diagnosis of numerous disorders on a single sample and through a single analytical process was possible. MS/MS allows for additional disorders to be added without a need for additional sample or analysis time. This allows rapid and high throughput analysis of samples at a very low cost. Today almost all developed countries have expanded NBS (eNBS) that screen from approximately 20-40 inherited metabolic disorders by MS/MS.[30] Expansion of NBS beyond PKU has revolutionized the diagnosis and treatment of metabolic disorders, greatly extending the concept of preventive medicine[31] and this success has resulted in the adoption of eNBS by many NBS programs worldwide.[31,32]

In 2001, an expert panel commissioned by the ACMG evaluated 84 candidate disorders and published in 2006 a universal and uniform list of disorders for NBS. The report defined a uniform panel of 29 core conditions and 25 secondary disorders. Forty of these 54 disorders are diagnosed by MS/MS. The rest of the disorders such as CH, CAH, biotinidase deficiency, and galactosemia are diagnosed by other methods. Recently, ADA-SCID, peroxisomal disorders, DMD, and some lysosomal storage disorders have also been added to this core panel for NBS.[33-35]

LABORATORY WORKFLOW AND MANAGEMENT IN A NBS LAB

A typical NBS laboratory receives approximately 100 to 1000 dried blood spots for analysis per day. The general turnaround time for analysis and reporting is usually 2–4 working days as in some diseases treatment must be started rapidly to prevent irreversible damage. For positive results, confirmatory tests are needed. The NBS laboratory also should implement quality management system. This must be in place to ensure the system's integrity in all phases – pre-analysis, analysis, and post- analysis. NBS laboratories are also a part of several activities such as education, public awareness, training, diagnosis, systematic follow-up, parental counseling, data management, and publications.

Box 2: NBS lab work flow

An NBS laboratory's activities are divided into three phases – pre-analytical, analytical, and post-analytical phases and many activities are involved between the arrivals of the samples for analysis till the reporting of results. Following points are based on the procedures followed at our laboratory, NIRMAN for Newborn Screening of 2 hospitals from South India.

Pre-analytical activities

To ensure accurate results in a NBS laboratory, it is very crucial to collect data such as time of sampling, delay between sampling and analysis, baby's condition (pre-maturity, gestational age, birth weight, para-enteral nutrition, transfusions, etc.) all of which can affect the NBS results. It is also important to check the quality of dried blood spots received so that the error is minimized. In addition to the method of sample collection, methods of storage and transportation also can lead to increase in errors in the results. Hence, it is very important that the NBS laboratory instructs and trains the primary physicians/hospital staff regarding the procedures of sample collection, storage, and transportation.

Sample collection

Few drops from a heel prick are taken on a filter card paper and air dried for few hours before sending them to the NBS laboratory. This filter paper card should be attached or should accompany a card which carries all the information of the baby including full name/unique number/bar code, date and time of birth, date and time of sample collection, birth weight, gestational age, mode of feeding (BF/TF), para-enteral nutrition if any, transfusions given if any, any other important information which may affect the results. Samples must be collected by heel puncture on the planar surface of the foot. Blood must completely fill the circles drawn on the filter paper and applied evenly. It must be air dried for 4 h at room temperature, before it is dispatched to the NBS laboratory.[36]

Time of sample collection

This is very important as it may affect some of the results and may result in some pre-analytical errors as some analytes vary with the infant's age. It is usual practice to collect samples for NBS between 24 and 72 h of age. Prematurity, birth weight, type of feeding, parenteral nutrition, neonatal jaundice, and some drugs may affect the levels of some metabolites.[37]

Transport

Samples should be sent to the NBS laboratory within 24 h of sample collection. Delays or harsh conditions during transport may result in degradation of some metabolites and result in false-negative results.

Once the samples arrive at the NBS laboratory, verification of sample card information, and validation of the dried blood specimen for quality and adequacy is performed. If insufficient or disqualified samples are detected then immediately they are recalled from the source hospitals/clinics.

Analytical phase

This phase is the most important phase. Given the large amount of samples to analyze in a timely and reproducible way, automation of some pre-analytical and analytical steps has been implemented at some NBS laboratories. Use of micro-volume pipetting station, automatic punchers, and bar code readers are used widely. Assays for the desired metabolites are performed and results generated. Accuracy of each assay is very important and hence each assay must involve use of quality control samples (low as well as high levels). For example, we participate in Centre for Disease Control and Prevention's (CDC) Newborn screening Quality Assurance Program (NSQAP) every year to maintain the quality of our analytical methods.

Post-analytical phase

After the analysis of the NBS samples is completed the laboratory needs to produce a report and determine if any of the samples needs confirmatory tests. As the disorders screened are rare, most of the results generated in a NBS program are normal. It is upon the policy of the NBS laboratory to decide the mode for notifying the results to the primary hospital. Most NBS laboratories (like our laboratory) issue reports for each sample analyzed. Some labs inform the primary hospitals only in case of positive results. Interpretation of results is to be done carefully and by a trained person with a sound knowledge of the metabolic disorders included in the NBS program. We have people trained at various universities in Europe in Metabolic disorders and have in-house confirmatory testing facility and management protocols.

NBS laboratories should participate in external control programs and exchange samples with reference laboratories. There are several quality assessment programs for NBS such as CDC NSQAP; College of American Pathologists; European Research Network for Evaluation and improvement of Screening, Diagnosis, Treatment of Inherited Disorders of Metabolism; and Reference institute for Bioanalysis.

The main aim is to reduce the number of false positive screening reports. False positive rate of < 0.3% and a positive predictive value of > 20 should be the target for any laboratory performing NBS.[38] Recall rate can be reduced by adjusting the cut-offs, second tier tests (e.g., MMA and propionylglycine if C3 elevated, alloisoleucine if leucine elevated) and use of one or more specific markers (e.g., succinylacetone in tyrosinemia type I rather than tyrosine).[39] Second tier testing allows to confirm the results with increased specificity on the same initial blood spot.

Positive results must be informed immediately to the referring hospital so that necessary action can be taken. However, every abnormal result should first be re-checked to ensure that the abnormal result is not due to pre- or analytical error. If it is still abnormal patient, should be recalled for testing. It is important to note that abnormal NBS results do not necessarily mean that the child has the disease, but it indicates the need for additional investigation before a final diagnosis can be reached. Due to inaccuracy of screening tests on DBS, it is important to note that NBS is not diagnostic and any positive result should be accompanied by diagnostic tests, preferably on a new sample for confirmation of the results of NBS, before any intervention is initiated. Newborns screened positive may then be referred to either the primary health care providers or directly to a tertiary specialized health facility. For treatment trained, metabolic pediatricians are necessary. Treatment is initiated only after an appropriate diagnosis is reached and parents are counseled regarding the possible outcome of the disorder. The ACT sheets developed by ACMG are useful for guidance in case of positive NBS results.[40]

IMPORTANCE OF NBS

In a recent study, it was shown that only 2% of cases detected by NBS had clinically severe outcomes compared to 42% of those detected clinically.[41] Clinically, diagnosed patients with several of the disorders have poorer outcomes than those with the same disorders identified by eNBS, including death, organ transplantation, poor developmental outcomes, and intellectual disabilities. Significantly better outcomes are seen in NBS detected patients when compared to clinically diagnosed patients.[41-44] Documented positive outcomes are in terms of lesser intellectual disabilities,[45] better IQs,[41] fewer deaths, and fewer disabilities.[42] Hence, NBS should be adopted as a policy in all countries to reduce the burden of individuals diagnosed with IEMs and other conditions. This will not only help in saving the cost for treatment and hospitalizations needed frequently in these disorders but also reduce the parental stress and anxiety, improving the quality of life for the patient and the family.

INDIAN SCENARIO

At present, there is no national NBS program in India. There is no doubt that NBS can save life, but NBS has not been accepted yet as a governmental policy in India. There is no comprehensible national strategy for implementation of a universal screening program and no guidance on which disorders should be included in the screening panel. Realizing the importance of NBS, ICMR in 2008 launched a pilot multi-center NBS program to screen 100,000 newborns for CH and CAH in 5 metropolitan cities – Chennai, Delhi, Hyderabad, Kolkata, and Mumbai. This study demonstrated the feasibility of NBS in Indian metropolitans.[25] In 2011, the national neonatology forum recommended CH, CAH, and G6PD as the screening panel to implement for NBS in

India.[46] Many small scale or pilot projects were started in India. However, of note among these were the Chandigarh Program, Kerala State NBS program, and Goa NBS Program. Union territory of Chandigarh started NBS for CH, CAH, and G6PD in 2007.[8] In 2008, Goa introduced mandatory expanded NBS for all newborns.[7] In 2009, West Bengal and in 2011 Gujarat governments have approved o launch large scale NBS program. However, these programs remain yet to be implemented. Now many private hospitals and labs offer this facility although at a cost and there is no insurance or government funding for this.

About 27 million babies are born every year in our country. Approximately 4:1000 and 5:1000 are estimated to have hearing defects and congenital heart abnormalities, respectively, whereas the incidence of IEMs in India is estimated to approximately 1:1000. This high incidence is due to high prevalence of consanguinity in our country. IEMs comprise approximately 15% of total admissions in NICUs annually. If undiagnosed and untreated many children develop mental retardation, learning disabilities, autism, dyslexia, behavioral abnormalities, and scholastic backwardness later in life. There is also considerable burden – financial and emotional on the parents to diagnose, treat, and manage these children. The most rational and cost-effective way of preventing such tragedies would be to have a NBS program which will detect most of the preventable or treatable, if not all IEMs and other disorders. Awareness of benefits of NBS is increasing and this could lead to the creation of one national NBS program. Although universal screening is a cost-intensive program, the benefits outweigh the cost as it helps in reducing the mortality and morbidity in these diseases.

CONCLUSION

All hospitals in urban areas in India should initiate NBS at least for the common disorders: CH, CAH, and G6PD deficiency. Expanded newborn screening may follow once these programs are well established and necessary infrastructure is in place. There is also a need to train more physicians in IEMs before expanded NBS is started.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Vitamin responsive conditions in pediatric neurology

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ABSTRACT

Vitamin responsive conditions can be either due to inherited defects in the metabolic pathways resulting in vitamin dependency or due to acquired deficiency states. Due to widespread malnutrition and predominantly vegetarian population in India, vitamin deficiency state is quite common and early identification is essential. Inherited defects, if treated earlier, lead to reduced morbidity and mortality and improvement in long-term neurocognitive outcomes. Various vitamin responsive conditions in pediatric neurology shall be discussed in this review. Infantile presentation of thiamine deficiency results in beriberi, and in adults, it leads to Wernicke's encephalopathy and Korsakoff psychosis. Biotin thiamine-responsive basal ganglia disease is a defect of thiamine transporter 2, which leads to neuroregression and characteristic neuroimaging features of basal ganglia involvement, it responds to high doses of biotin and thiamine. Riboflavin is an enzyme involved in mitochondrial energy synthesis and is supplemented in various mitochondrial metabolic conditions. Brown-Vialetto-Van Laere syndrome is progressive pontobulbar palsy caused by defect in riboflavin transporters responsive to high doses of riboflavin. Pyridoxine responsive epilepsy presents with pharmacoresistant seizures in neonatal or early infantile age, biotinidase deficiency also presents with similar neurological manifestations, but typical cutaneous symptoms of rash and seborrheic dermatitis also occur. Both are epileptic encephalopathies and any infant presenting with epilepsy not responding to conventional AEDs must be given a trial of pyridoxine, biotin, and folinic acid. Vitamin B12 responsive conditions can include deficiency states, such as those manifesting with peripheral neuropathy and the syndrome of infantile tremor syndrome (developmental delay or regression, tremors, and megaloblastic anemia) as well as inherited disorders of homocysteine and cobalamin metabolism. These disorders are differentiated on the basis of clinical phenotype and laboratory parameters (serum B12, homocysteine levels, methylmalonic acid levels, etc.). Infantile tremor syndrome responds drastically to mega doses of Vitamin B12 and other multivitamins. Vitamin E deficiency causes ataxia with Vitamin E deficiency, other vitamins which can neurological symptoms include Vitamin C (pseudoparalysis) and Vitamin K (central nervous system bleeds). It is imperative for a practicing pediatrician to be well versed with these conditions, as these are potentially treatable conditions.

Keywords: Vitamins, Vitamin responsive epilepsies, Vitamin B12, Thiamine, Biotin

INTRODUCTION

Vitamins are naturally occurring food substances that are essential for the proper functioning of the human body in small quantities. Most of the time, they act as cofactors for various enzymatic reactions. Vitamin responsive conditions can be either due to inherited defects in the metabolic pathways resulting in vitamin dependency or due to acquired deficiency states. The nervous system, being one of the highly metabolically active systems of the human body, shows early and more severe manifestations of vitamin responsive conditions. In this review, we shall briefly discuss the various vitamin responsive conditions in pediatric neurology. A host of other disorders both acquired and inherited respond to vitamins and cofactors and the reader is referred to some good recent articles on this subject.[1]

THIAMINE (B1)

Thiamine is a water-soluble, sulfur-containing vitamin involved in key reactions of mitochondrial energy synthesis. Pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and branched-chain alpha-keto acid dehydrogenase are the three enzymes for which thiamine is required as a cofactor. Deficiency usually occurs in malnutrition and malabsorptive states. Infantile presentation of thiamine deficiency results in beriberi, which is of two types. In dry beriberi, there is length-dependent sensorimotor peripheral neuropathy without cardiac involvement. Wet beriberi is characterized by neuropathy as well as cardiac involvement in the form of systolic dysfunction and cardiac failure. Wernicke's encephalopathy and Korsakoff's psychosis are commonly seen in alcohol-dependent adults. In children, gastrointestinal surgical procedures, recurrent vomiting, chronic diarrhea, cancer and chemotherapy, systemic diseases, drugs, and malnutrition can result in manifestations like Wernicke's encephalopathy. The classic triad consists of encephalopathy, oculomotor dysfunction, and gait ataxia but is not seen in all patients. Manifestation such as these in young particularly malnourished children after an episode of vomiting, diarrhea should prompt its consideration.[2]

Common magnetic resonance findings include symmetric T2 hyperintensities in dorsal medial thalamus, mammillary bodies, brain stem, and basal ganglia structures.[3] Treatment with thiamine (infants IV 25–50 mg followed by 10 mg IM for a week and 3–5 mg once a day orally for 6 weeks; children 10 mg IM/IV for the 1st week, then 3–5 mg orally for 6 weeks; and adolescents 100 mg IM/IV once a day for 1 week then 10 mg orally once a day)[4-6] should be instituted immediately when the diagnosis is suspected.[7]

BIOTIN THIAMINE-RESPONSIVE BASAL GANGLIA DISEASE

Most commonly reported from Saudi Arabia, this disease is known by several names such as "Thiamine metabolism dysfunction syndrome Type 2," "SCL19A3 gene defect," and "biotin-responsive basal ganglia disease" "biotin thiamine-responsive basal ganglia disease." The primary defect is in the thiamine transporter 2, encoded by the autosomal recessive SLC19A3 gene. This disease usually presents in childhood with an episode of neuroregression following a non-specific trigger such as febrile viral illness or trauma. Clinical manifestations include subacute encephalopathy, seizures, cranial nerve palsies, extrapyramidal symptoms, and quadriparesis. Rarely, infantile Leigh like the picture, as well as adult Wernicke's encephalopathy, has also been described to be associated with this disease. MRI picture during the acute episode includes vasogenic edema in the basal ganglia region (caudate and putamen), as well as signal changes in the thalamus and white matter, later on, atrophy, which may ensue. Treatment includes high doses of biotin and thiamine (5–10 mg/kg of thiamine and 10–40 mg/kg of biotin) in the acute stages and lower doses of thiamine in the chronic stage. Prognosis depends on the age of onset, rapidity of treatment, and the clinical severity.[8]

RIBOFLAVIN (B2)

Riboflavin or B2 is a water-soluble vitamin predominantly involved in various oxidation-reduction reactions as flavin adenine dinucleotide or flavin mononucleotide. It plays an important role in the citric acid cycle, electron transport chain, beta-oxidation, and degradation of amino acids. Deficiency states include glossitis, cheilitis, seborrheic dermatitis, anemia, and axonal variety of sensory-motor neuropathy.[9] Riboflavin being an important component of the electron transport chain, it is hypothesized that riboflavin supplementation reduces cell death and necrosis in mitochondrial disorders. Various disorders potentially responsive to riboflavin include multiple sclerosis, Parkinson's disease, Alzheimer's disease, migraine, multiple acyl dehydrogenase deficiency, mitochondrial complex deficiencies, glutaric aciduria, Leber's hereditary optic neuropathy, Alpers syndrome, and Kearns-Sayre syndrome.[10]

BROWN-VIALETTO-VAN LAERE (BVVL) SYNDROME

Mutations in the riboflavin transporter genes SLC52A2 and SLC52A3, which encode riboflavin transporters, cause autosomal recessive inherited neurodegenerative disorders BVVL and Fazio Londe (FL) syndrome. This syndrome is characterized by progressive pontobulbar palsy (ataxia secondary to axonal sensorimotor neuropathy and weakness of upper limbs), nystagmus, sensorineural hearing loss (not in FL syndrome), and respiratory insufficiency. Brain MRI may be normal or may demonstrate brainstem changes. Significant improvements have been reported to occur following supplementation with high-dose riboflavin.[11] High-dose riboflavin is reserved for the treatment of metabolic defects in which riboflavin is a cofactor. These include a host of mitochondrial disorders, glutaric aciduria, and patients with mutations in the riboflavin transporter genes.

PYRIDOXINE

Pyridoxine or Vitamin B6 is a cofactor for multiple enzymatic reactions and has an important role in dopamine synthesis, serotonin synthesis, homocysteine metabolism, and conversion of glutamate to glutamate and gamma-

aminobutyric acid. Pyridoxine deficiency may manifest as neuropsychiatric symptoms of anxiety and depression, sensorimotor polyneuropathy, dermatological manifestations such as seborrheic dermatitis, glossitis, cheilosis, and hematological manifestations like sideroblastic anemia. Pyridoxine deficiency may be caused by malnutrition, malabsorptive states, drugs such as isoniazid, and anti-seizure medications (phenytoin and carbamazepine). Isoniazid therapy causes a neuropathy that is reversible with pyridoxine therapy.

PYRIDOXINE-DEPENDENT EPILEPSY (PDE)

This disorder commonly presents with neonatal-onset epileptic encephalopathy unresponsive to AEDs but responsive to pyridoxine. The defect is in the lysine metabolism due to autosomal recessively inherited mutations in the ALDH7A1 gene, which encodes antiquitin or a-aminoadipic semialdehyde (aAASA) dehydrogenase. Deficiency of this enzyme results in the accumulation of aAASA/L-D1-piperidine-6 carboxylate (P6C) in the body fluids, which inactivates pyridoxal phosphate (PLP). Clinical manifestations include excessive intrauterine movements, which are actually intrauterine seizures, neonatal seizures, gastrointestinal symptoms, and developmental delay. Presentations beyond early infancy are rare, although they may occur. Neuroimaging may be normal or may show corpus callosum anomalies, ventriculomegaly, delayed myelination or hypoplasias, etc. Diagnosis is made by elevated levels of alpha-aminoadipic semialdehyde, P6C, and pipecolic acid in urine and cerebrospinal fluid (CSF), although genetic diagnosis is confirmatory. PDE is a treatable cause of epilepsy; hence' any neonate presenting with unexplained refractory seizures should be given a trial of Vitamin B6. In a seizing infant, 100 mg of pyridoxine given intravenous results in clinical as well as an electrographic response; however, every infant should be given a trial of oral supplementation even if there is no response to the intravenous trial. The risk of side effects like apnea should be kept in mind while administering pyridoxine. The usual dose is 15–30 mg/kg, long-term poor outcome in the form of developmental delay and neurological sequelae occurs even with cessation of seizures. Prophylactic treatment with pyridoxine has been advised for *in utero* treatment of suspected or proven PDE children. Some patients of PDE respond not only to pyridoxine but also to folinic acid, as both of these disorders are allelic. PNPO deficiency, which occurs due to a defect in pyridoxal 5-phosphate oxidase, responds to PLP (pyridoxal 5-phosphate) rather than to pyridoxine; this entity is known as pyridoxal 5-phosphate responsive epilepsy. Potential treatment options also include lysine restriction and arginine supplementation, which have a possible role in improving long-term neurodevelopmental outcomes, although the evidence currently is limited.[12,13]

BIOTIN

Biotin or Vitamin B7 is a cofactor for pyruvate carboxylase, propionyl-Coa carboxylase, beta-methylcrotonyl-Coa carboxylase, and two isoenzymes of acetyl-Coa carboxylase. It is involved in the key reactions of gluconeogenesis, fatty acid synthesis, and amino acid catabolism. Pathogenesis of the central nervous system (CNS) involvement is unknown, and as such dietary deficiency is rare. Two disorders that result in biotin deficiency are multiple carboxylase deficiency and biotinidase deficiency.

BIOTINIDASE DEFICIENCY

Another form of vitamin responsive condition is biotinidase deficiency. Biotinidase is an enzyme that recycles biotin in the human body. Biotinidase deficiency is an autosomal recessive inherited disease resulting in two types, profound deficiency (1–10% of enzyme activity) and the partial deficiency (10–30% of enzyme activity). Affected children present between neonatal age to early childhood with neurocutaneous features such as seizures (generalized, partial, spasms, and myoclonic), rash, seborrheic dermatitis, hypotonia, developmental delay, and vision and hearing impairment. Laboratory studies show elevated CSF and blood lactate and pyruvate levels, organic acidemia, and urinary excretion of 3-hydroxyisovaleric acid. EEG may show severe abnormalities such as burst suppression or multifocal spikes [Figure 1]. Neuroimaging is non-specific; delayed myelination and cortical atrophy may be present. This disease responds to pharmacologic doses of biotin (5–10 mg/day), and seizures have been known to become passive by 24–48 h of administration of biotin. Recently, screening for biotinidase deficiency has been advocated in multiple neonatal screening programs, as the prompt administration of biotin improves the long-term neurocognitive outcomes.[14]

VITAMIN B12 AND FOLATE

Vitamin B12 and folate are involved in various important metabolic reactions and have protean manifestations of their deficiency and dependency states. Response to these cofactors is seen not only in the disease of a defect in their metabolic pathway but also in related other metabolic conditions. These disorders are complex; however, a brief review shall be done here, highlighting important diseases.

VITAMIN B12 METABOLISM

Vitamin B12 is found in non-vegetarian sources such as meat, milk, and eggs. Vegetarian diets are deficient in

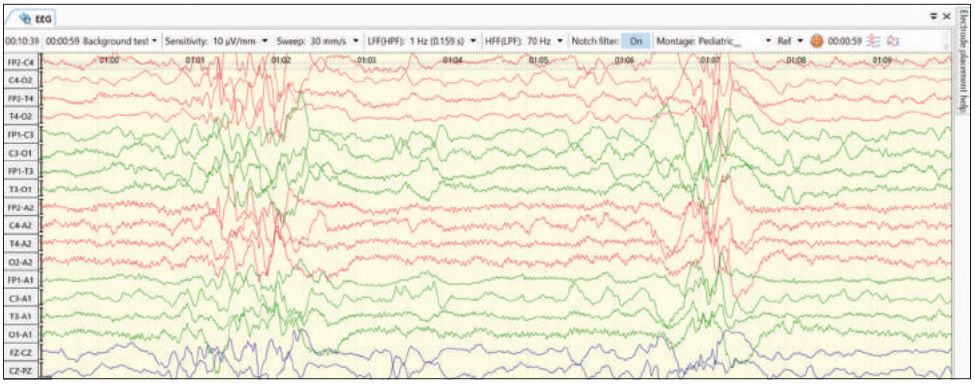

Figure 1: EEG abnormality with features like hypsarrhythmia in an infant with biotinidase deficiency.

Vitamin B12. Vitamin B12 bound to food sources is released in the stomach by peptides, and it binds to haptocorrin. In the duodenum, the Vitamin B12-haptocorrin complex is broken, and Vitamin B12 is bound to the intrinsic factor; this is the complex which is absorbed in the distal ileum. In the blood circulation, B12 is bound to haptocorrin and transcobalamin; transcobalamin is the cellular delivery protein.

Vitamin B12 acts as a cofactor for two enzymes, methionine synthase, which converts homocysteine to methionine, and methylmalonyl-CoA mutase, which converts methylmalonyl-CoA to succinyl-CoA. The deficiency of Vitamin B12 results in the involvement of two major organ systems, hematologic, resulting in megaloblastic anemia and neurologic, as B12 is essential for the formation and maintenance of normal myelination.

Dietary deficiency of Vitamin B12 occurs commonly in adults due to pernicious anemia; however, this cause is rare in children. Children commonly suffer due to causes such as increased metabolic demands, malabsorptive states, and nutritional deficiencies. Vitamin B12 deficiency manifests as megaloblastic anemia, hypercellular marrow, pancytopenia, peripheral neuropathy, myelopathy, optic atrophy, and CNS symptoms.[15]

INFANTILE TREMOR SYNDROME (ITS)/ NEUROCUTANEOUS SYNDROME OF VITAMIN B-12 DEFICIENCY (NIB SYNDROME)

This disorder is usually seen in infants of vegetarian mothers who are themselves deficient in B12. The usual age of presentation is 6–12 months; however, this disorder can present as developmental delay from early infancy to later in the 2nd year of life. Symptoms include the triad of developmental delay or regression, tremors, and megaloblastic anemia. The affected infant has a characteristic phenotype; predominantly breastfed, they become progressively listless and apathetic, lose interest in surroundings, develop a bleating cry, chubby appearance, sparse, thin lustreless hair, and hyperpigmentation in limbs [Figures 2 and 3]. Tremors though characteristic are not seen in majority of the children. It has been shown that tremors predict poorer long-term developmental outcomes and hence indicate a more severe and prolonged deficiency of Vitamin B-12.[16] A new terminology has been suggested for this syndrome "NIB syndrome" highlighting the central role of Vitamin B-12 deficiency in its occurrence.[17] It is hypothesized that B12 is essential for normal maturation and myelination in the human brain, and hence, its deficiency results in these symptoms. MRI shows variable changes including atrophy, delayed myelination, as well as signal changes over the basal ganglia in severe cases.[18] Serum Vitamin B12 assays have low sensitivity and specificity as the major form of B12 in the serum is bound to haptocorrin; however, B12, which is available at the tissue level, is the one bound to transcobalamin. Homocysteine also increases; however, the elevation of homocysteine is seen in a variety of other conditions related to homocysteine and folate metabolism; hence, the most specific and sensitive marker of B12 deficiency currently available is the elevation of methylmalonic acid in urine and serum. In practice, however, homocysteine is easily available and can be considered as the most important surrogate marker of Vitamin B-12 deficiency. The characteristic feature of ITS is the rapid and marked response to Vitamin B12 supplementation. Improvement in appetite occurs; the infant becomes less irritable and more playful, and gradually, neurological symptoms abate. The usual dose is 1000 mcg of Vitamin B-12 given intramuscularly for 7–14 days till there are clear signs of recovery. This is followed by dosing that is less frequent, alternate days, and then once a week. Monthly doses may be given to see that the deficiency does not recur and to cover the crucial periods of recovery. Along with Vitamin B12, they should be supplemented with iron, folic acid, Vitamin D, calcium, and other multivitamins as many times deficiencies coexist.[17,19]

INHERITED DISORDERS OF INTRACELLULAR COBALAMIN METABOLISM

These are a group of conditions that are all autosomal recessively inherited. They present with a myriad of organ

Figure 2: Sparse hair in a child with nutritional Vitamin B-12 deficiency (infantile tremor syndrome).

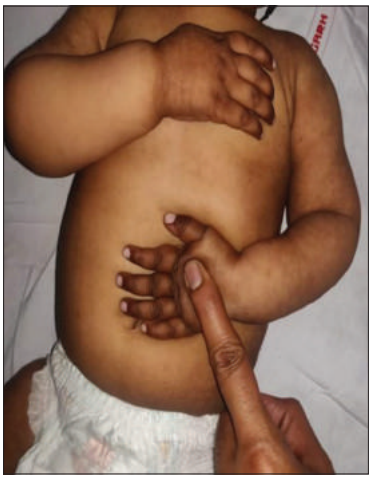

Figure 3: Hyperpigmentation in a child with infantile tremor syndrome, note the pigmentation on dorsum of hands and reticular pigmentation of arms and forearms.

involvement and brain is commonly affected. The disorders either cause isolated homocystinemia, or methylmalonic acidemia or combined homocystinemia and methylmalonic acidemia. Vitamin B-12 is used lifelong to treat these inborn errors of cobalamin pathway with variable benefit.

INHERITED VITAMIN RESPONSIVE DISORDERS PRESENTING WITH ELEVATED HOMOCYSTEINE

Three major disorders in this category include classic homocystinuria due to cystathionine beta-synthase deficiency, combined defects of homocysteine, and methionine and methylenetetrahydrofolate reductase (MTHFR) mutations. All these disorders can present with predominant CNS symptoms such as seizures and mental retardation. Differentiation can be made based on levels of methionine and methylmalonic acid; classic homocystinuria shall have elevated methionine with normal methylmalonic acid levels. Classic homocystinuria responds to pyridoxine, folinic acid, dietary methionine restriction, betaine supplementation, and Cblc defects, and MTHFR deficiency responds to high-dose betaine, hydroxocobalamin, methionine, pyridoxine, and riboflavin.[20]

CEREBRAL FOLATE DEFICIENCY

It is a neurological syndrome associated with a low CSF 5-MTHF in the presence of normal folate metabolism outside the nervous system. This disorder usually presents in infancy with regression, developmental delay, and seizures. The defect is in the impaired folate transporter inside the CNS. This disease responds to oral folinic acid. Secondary forms of cerebral folate deficiency include chronic use of antifolate and anticonvulsant drugs and other conditions such as Rett syndrome, Aicardi-Goutières syndrome, and Kearns-Sayre syndrome.[21]

VITAMIN E

Vitamin E deficiency occurs in chronic malabsorption states such as malabsorption syndromes, cystic fibrosis, and abetalipoproteinemia and manifests with progressive weakness, ataxia, ophthalmoplegia, and loss of position and vibration sense. Treatment consists of usual supplementation with Vitamin E; abetalipoproteinemia usually responds to large doses.

Ataxia with Vitamin E deficiency is usually seen in childhood to early adulthood with clinical features of ataxia, cerebellar signs, areflexia, and neuropathy. Diagnosis is made by the characteristic phenotype along with reduced levels of alpha-tocopherol in serum in the presence of normal levels of lipoproteins and exclusion of malabsorption syndromes. Genetic diagnosis is confirmatory, which shows biallelic pathogenic variations in the TPPA gene.[22]

OTHER VITAMINS

Vitamin C deficiency is now not frequent and is generally seen in malnourished children. It can also occur in children with disabilities or peculiar diets and dietary preferences. Scurvy occurs in severe Vitamin C deficiency and can present with pseudoparalysis. Apart from Vitamin C, Vitamin-K deficiency is also not infrequent despite widespread use of Vitamin-K at birth. Infants present with bleeding manifestations and intracranial hemorrhages can occur [Figure 4]. Infants present with pallor, lethargy, and seizures. Signs of raised ICP like bulging anterior fontanelle are not infrequent.

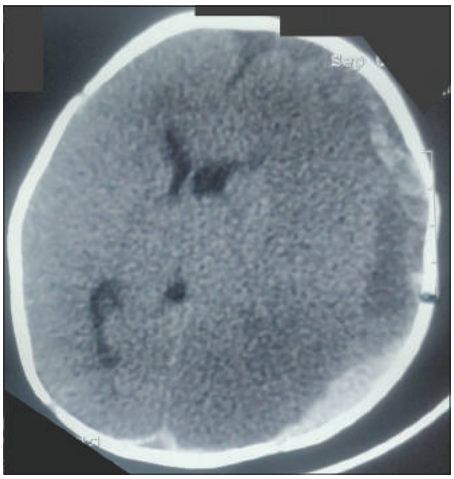

Figure 4: Plain CT head in an infant with Vitamin K deficiency, large subdural bleed on the left side (black arrow, note the separation of serum and clot giving two density appearances of the bleed), with secondary ischemic changes and midline shift. The baby had presented with pallor, coma, and bulging non-pulsatile anterior fontanelle.

CONCLUSION

For any practicing pediatrician, it is vital to be aware of conditions that are responsive to vitamins. This review presents an overview of some common disorders which are vitamin responsive. However, this list is not exhaustive. It is vital to remain abreast with evolving information of this subject. It is not possible or desirable to remember all such conditions many of which are exceedingly rare. It is crucial that consultation is sought from specialists who have more experience in handling such patients. Many times, the treatment with vitamins is begun empirically awaiting laboratory results. This approach is justified and can prevent and limit disability in affected children.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Epileptic Spasms-West syndrome secondary to Dravet syndrome due to *SCN* gene mutation from India

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ABSTRACT

Objectives: West syndrome (WS) is a triad of epileptic spasms, developmental delay/regression, and hypsarrhythmia. SCN related epileptic encephalopathy is a rare epilepsy syndrome characterized by an early-onset, severe, and epileptic encephalopathy. The causes of WS are multiple and diverse ranging from genetic to structural, metabolic, and unknown causes. The objectives of the study were to report SCN related epileptic encephalopathies with epileptic spasms.

Materials and Methods: This is retrospective chart review of children presenting with epileptic spasms secondary to *SCN* gene variants from January 2015 to March 2020 in a tertiary care referral center.

Results: Out of 15 children, ten were boys. The mean age of presentation was 5 months. Thirteen children had preceded seizures before epileptic spasms in the 1st year of life, two children presented initially with epileptic spasms. No neuro-deficits were noted in all the children. In all the cases electroencephalogram was suggestive of hypsarrhythmia. Routine testing, neuroimaging, and metabolic tests were normal in all the cases. Various pathogenic variants seen in next-generation sequencing were *SCN1A* in 11, *SCN1B* and *SCN2A* in two children each. Three children responded for vigabatrin and five children responded for steroids but all of them had relapse and were refractory to other antiepileptic drugs.

Conclusion: *SCN* related epileptic encephalopathy should be considered in the differential diagnosis of epileptic spasms. These infants present earlier compare to classical Dravet syndrome children.

Keywords: Epileptic spasms, West syndrome, *SCN* mutation, Epileptic encephalopathy

INTRODUCTION

Dravet syndrome (DS) and *SCN* related encephalopathies are genetically determined severe early onset epileptic encephalopathy (EOEE), which begins in the 1st year of life in an otherwise normal infant.[1] Initial seizures, often induced by a fever, tend to be prolonged generalized or unilateral tonic and/or clonic seizures, are more frequent and come in clusters. Beyond the 1st year, multiple seizure types often develop such as myoclonic, atypical absence, and focal seizures. West syndrome (WS) is the most common epilepsy syndrome in infancy, which is characterized by triad of infantile spasms, developmental deterioration, and hypsarrhythmia.[2] It can be due to structural, genetic, infectious, immune, metabolic and unknown cases. Several genes, such as,

SCN1A, *SCN2A*, *SCN1B*, *ATXN2*, *NR3C1*, *KPNA7*, *STXBP1*, *ABCB1*, *GRIN1*, *ARX*, and *TSC2,* were found to be associated with the pathogenesis of epileptic spasms.[3] Variants in the gene encoding voltage-gated sodium channel (*SCN1A*) are associated with several epilepsy syndromes. Here, we report children of *SCN* related epileptic encephalopathies who presented with epileptic spasms.

MATERIALS AND METHODS

This is a retrospective chart review of epileptic spasms due to *SCN* related epileptic encephalopathies from tertiary care referral center, from southern part of India. The medical records of children attending the pediatric neurology clinic and those who were admitted in pediatric neurology and pediatric ward from January 2015 to March 2020 were analyzed. Among them, only children who were confirmed to have a diagnosis of *SCN* related epileptic encephalopathies in genetic studies and presented with epileptic spasms were included and formed the study group. Those children with epileptic spasms and suspected *SCN* related epileptic encephalopathies without genetic confirmation were excluded from the study. The data were extracted as per-designed pro forma. Details of history including birth history, developmental history, clinical features including seizure semiology, precipitation of seizures with fever, investigations such as complete hemogram, liver function, renal function, serum calcium, serum ammonia, serum lactate, arterial blood gas, and neuroimaging MRI of brain were taken. Special investigations such as tandem mass spectrometry (TMS), electroencephalogram (EEG), and genetic analysis were also taken. Statistical analysis was performed with SPSS version 21. The results were analyzed. Ethical clearance was obtained, from institutional ethical committee.

RESULTS

A total of 50 children with *SCN* related epileptic encephalopathies were seen during this period, out of these 15 (35%) had epileptic spasms. The various clinical features, laboratory findings, and outcome of all the 15 children are mentioned in [Table 1]. Of the 15 children, ten (67%) were boys. All of them presented in 1st year of life except once child, with mean age of presentation being 5 months of age compare to 10 months in children with *SCN* related epileptic encephalopathies without epileptic spasms. All of them presented with other seizures in the form of focal or generalized seizures along with epileptic spams, and except two children who had only epileptic spasms as per history. Seven children presented with fever triggered seizures and spasms, four children presented with seizures after vaccination and four children had afebrile seizures before onset of spasms. Birth history was normal in all the children. Initial development was normal followed by severe developmental delay in all the children. Neuro imaging and TMS were normal in all the children. EEG showed hypsarrhythmia in all the children. EEG showing modified hypsarrhythmia in [Figure 1]. Targeted next generation sequencing showed *SCN1A* gene mutation in 11 children, *SCN1B* and *SCN2A* in two children each. Spasms were controlled initially with vigabatrin and steroids, but later seizures were refractory to treatment.

DISCUSSION

There are only few reports describing *SCN* related epileptic encephalopathies presenting with epileptic spasms secondary to mutation in *SCN* gene in the literature. Here, we are reporting 15 patients presenting as WS with mutation in *SCN* gene. Around 70–80% of children with *SCN* related epileptic encephalopathies have point mutations or gross rearrangements in the *SCN1A* gene. Over 1200 variants associated with epilepsy have been reported in *SCN1A*.[4] Truncating variants are associated with severe phenotypes. The missense variants are associated with a wide spectrum of phenotypes from DS to much milder forms of epilepsy, such as febrile seizures and "febrile seizures plus," which are often familial and part of a genetic epilepsy with febrile seizures plus.[5] Ten percent of *SCN* related epileptic encephalopathy patients have deletion, duplication, or amplification identified with multiplex ligation-dependent probe amplification. In 10–20% of cases, the genetic cause remains unknown, may be other genes are likely to be involved. Less than 1% of *SCN* related epileptic encephalopathy patients have homozygous mutation in *SCN1B*, and very few have *GABRG2* or *SCN2A* mutations.[6]

WS is an epileptic encephalopathy with onset typically around 6 months of age, characterized by epileptic spasms, hypsarrhythmia, and developmental delay or regression.

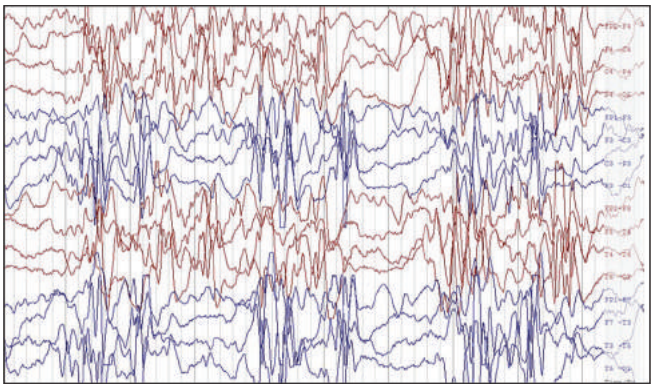

Figure 1: Electroencephalogram of bipolar longitudinal montage with a sensitivity of 20 μV showing high amplitude multifocal spikes, sharp waves with secondary generalization followed by suppression suggestive of modified hypsarrhythmia in a 8-months-old child with epileptic spasms due to *SCN1A* pathogenic variant.

Table 1: Various clinical and laboratory profile of study population.

Case number	Sex	Age of onset (m.)	Fever triggered seizures	Seizure type	Last follow-up (mo.) and Dev	Gene	Variant	AED tried	Response to AED
1.	M	3	No	GTCS, ES	45 NA	*SCN1A*	Ex16.c.3199G>A/p. Ala1067Thr	VPA, LEV,CZM, TPM, ZSM, VB, ACTH	VB
2.	M	3	Yes	Focal, ES	42 NA	*SCN1A*	Ex8.c.3199G>A/p. Ala1067Thr	VPA, LEV,CZM, TPM, ZSM, VB, ACTH	ACTH
3.	M	16	Yes	ES	37 Amb Autistic	*SCN2A*	Ex7.c.823C>T/p. Arg275Ter	VPA, CBZ, LEV, CZM, TPM, ZSM, VB,ACTH	VB
4.	M	3	No	GTCS, F, ES	60 NA	*SCN1A*	c.6013C>T/p. Arg2005Cys	VPA, SP, LEV, CZM, TPM, ZSM, VB, ACTH	None
5.	F	2	Yes	GTCS, F, ES	13 NA	*SCN1A*	Ex8.c.3199G>A/p. Ala1067Thr	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	ACTH
6.	F	3	Yes	GTCS, F, ES	07 Amb Autistic	*SCN1B*	c.253C>T/p.Arg85 Cys	VPA, SP, LEV, CZM, TPM, ZSM, VB, ACTH	SP
7.	F	3	Yes	GTCS, F, ES	48 NA	*SCN1A*	c.3199G>A/p. Ala1067Thr	VPA, SP, LEV, CZM, TPM, ZSM, VB,ACTH	None
8.	M	3	Yes	GTCS, F, ES	12 Autistic	*SCN1A*	c.3199G>A/p. Ala1067Thr	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	ACTH
9.	M	9	Yes	GTCS, F, ES	33 NA	*SCN2A*	c.823C>T/p. Arg275Ter	VPA, CBZ, LEV, CZM, TPM, ZSM, VB, ACTH	CBZ
10.	M	3	Yes	GTCS, F, ES	28 Amb Autistic	*SCN1A*	c.695G>T/p. Gly232Val	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	ACTH
11.	M	5	Yes	GTCS, F, ES	25 NA Autistic	*SCN1A*	c.3199G>A/p. Ala1067Thr	VPA, SP, LEV, CZM, TPM, ZSM, VB, ACTH	SP
12.	F	1	Yes	GTCS, F, ES	12 NA Autistic	*SCN1A*	Ex26.c.4907G>A/p. Arg1636Gln	VPA, SP, LEV,CZM, TPM,ZSM, VB,ACTH	None
13.	F	7	Yes	GTCS, F, ES	21, Amb Autistic	*SCN1A*	Ex26.c.4855A>G/p. Met1619Val	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	ACTH
14.	M	6	Yes	GTCS, F, ES	24 NA Autistic	*SCN1A*	Ex15.c.2712dupT/p. Ala905Cysfs	VPA, SP, LEV, CZM, TPM, ZSM, VB, ACTH	None
15.	M	8	Yes	ES	18 NA, Autistic	*SCN1B*	c.560delG/p. Arg187profs	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	VB

ACTH: Adrenocorticotropic hormone, AEDs: Antiepileptic drugs, Amb: Ambulatory, CLB: Clobazam, CBZ: Carbamazepine, DEV: Development, ES: Epileptic Spasms, F: Focal, GTCS: Generalized tonic-clonic seizures, LEV: Levetiracetam, NA: Non ambulatory, SP: Stiripentol, VPA: Valproate, TPM; Topiramate, VB: Vigabatrin, ZNS: Zonisamide

Etiology of epileptic spasms is widely heterogeneous, with acquired and congenital causes. Advances in the genetic investigations have led to discovery of new genes in WS in the past few decades. More than ten genes had been shown to be associated with epileptic spasms.[7] More recently, copy-number variations and mutations in *STXBP1*, *SCN2A*, and *KCNQ2*, which were previously associated with EOEE, have been found in patients with epileptic spasms.[8] Despite these advances, in many cases the cause still remained hidden.[9] The study done by Wallace *et al*. extends the phenotypic heterogeneity of mutations in *SCN1A* to include epileptic spasms.[10]

In seven children initial seizures were noticed following DPT vaccine and subsequently developed epileptic spasms, this finding was consistent with other studies of seizures following vaccinations which were reported in 7–57% of children with DS.[11,12] Two children presented with epileptic spasms one had *SCN2A* and the other with *SCN1B* mutation.

Ogiwara *et al*.[13] reported mutation in *SCN2A-E1211K*, causing epileptic spasms. Nakamura *et al*.[14] reported, nine of 67 Ohtahara syndrome (OS) cases (13.4%) and one of 150 WS cases (0.67%) were secondary to *SCN2A* mutation. All nine mutations in patients with OS were in linger regions between two transmembrane segments. In seven of the nine patients

with OS, EEG findings transitioned from suppression-burst pattern to hypsarrhythmia.

Harkin *et al*.[15] described missense *SCN1A* variant, Nav1.1-p. Thr226Met (T226M) is associated with a far more profound clinical phenotype than typical DS, represents a new class of early infantile epileptic encephalopathy (EIEE) located even beyond DS on the classical severity spectrum of *SCN1A*-linked disorder. Sadleir *et al*.[16] described the clinical presentation of more severe *SCN1A*-linked "early infantile *SCN1A* encephalopathy." They identified eight unrelated cases with an identical, presumed *de novo* missense variants resulting from c.677C > T in *SCN1A* exon 5. A ninth unrelated child, with the *de novo SCN1A* missense variant p.Pro1345Ser (c.4033C > T), was also included in the series due to the similarities in symptomology to the T226M patients indicates that early infantile *SCN1A* encephalopathy can arise from more than one particular variant. In our study, none of them had T226M variant, but most common variant is A1067T.

The mean age of presentation is our study was 5 months; however, mean age of presentation for A1057T variant is 3 months. Mean age of presentation of 50 children with *SCN* related epileptic encephalopathies with or without epileptic spasms was 10 months. Males are most affected. Only four of them are ambulatory, ten of them had autistic features. Epilepsy is refractory in all children, however epileptic spasms responded for steroids in five and vigabatrin in three children but later relapsed and refractory requiring polytherapy. Six children received stiripentol but only partial response that is more than 50% reduction in seizures noted in two children. We tried carbamazepine, sodium channel blocker in *SCN2A* subtype but only partial improvement was noted.

Traditional DS can be differentiated from early infantile *SCN1A* encephalopathy in several ways.[16] Early infantile *SCN1A* encephalopathy has an earlier age of onset, with seizures arising at an average of 9 weeks of age, more profound developmental impairments; and the majority required feeding tubes. Early infantile *SCN1A* encephalopathy presents with hyperkinetic movements, as early as 9 weeks of age and epileptic spasms, neither of which are seen in patients with DS, while hyperkinetic movements are not characteristic of *SCN1A* linked DS. However, similar movements are described with *SCN2A* and *SCN8A*-linked EIEEs; this overlap in symptomology led Sadleir *et al*. to speculate that the early infantile *SCN1A* encephalopathy, such as *SCN2A* and *SCN8A*-linked EIEEs, may be associated with a gain-of-function variant.

Epileptic spasms can be present in *SCN* mutations. They present earlier than classical DS with more severe developmental delay and refractory to treatment. Most common pathogenic variant noted in this study is A1057T in *SCN1A*.

CONCLUSION

In all cases of unexplained epileptic spasms, one should consider possibility of *SCN* gene mutation and genetic testing should be considered. Most common type of *SCN1A* mutation is A1057T variant. Early identifications are useful to select antiepileptic drugs for this subgroup of epileptic spasms.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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Karnataka Pediatric Journal

Case Report

Status dystonicus in children: Treat the precipitating factors

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ABSTRACT

Status dystonicus (SD) is a life-threatening movement disorder associated with significant morbidity and requires immediate and urgent intervention. It usually develops from both primary and secondary dystonias and rarely can be a complication of symptomatic insults such as infections, brain insults, or drugs. Compared to adults, it is seen more commonly in children due to the risk of many trigger factors and vulnerability of the developmental brain. Due to the delay in the identification and prevention of the triggering factors, nowadays most children require intensive care. Here, we report a 1-year-old boy, who was a known case of dyskinetic cerebral palsy, presented with increased twisting movements after an episode of febrile illness. The SD partially resolved after midazolam infusion, however, after treating the triggering factors (constipation and pneumonia), the SD resolved completely.

Keywords: Status dystonicus, Kernicterus, Dyskinetic cerebral palsy

INTRODUCTION

Status dystonicus (SD) was first described by Jankovic and Penn as "an uncommon neurological emergency with acute worsening of dystonia requiring urgent hospital admission." It is called by various other names such as dystonic storm, life-threatening dystonia, and desperate dystonic. Dystonia usually worsens as a continuum spectrum ranging from pre SD to SD. Different drugs had been used to alleviate dystonia through muscular relaxation, sleep sedation, and reduction of pain due to muscular contraction. However, unless the precipitating factor is taken care of, the status dystonia does not resolve and may progress to severe rhabdomyolysis. We here, describe a 1-year-old boy presenting with severe SD and subsided after treating the precipitating factors.

CASE REPORT

A 1-year-old boy presented with fever, increased work of breathing, and increased twisting posturing episodes each lasting for 30 min to 1 h for the past 4 days. The child was born at term with a smooth perinatal transition. There was a history of jaundice on day 2 of the birth with bilirubin levels maximum up to 40 mg/dl. He required double-volume exchange transfusion and phototherapy with which jaundice resolved. He had partial neck control, recognizes mother but cannot sit with support, and also does not respond to auditory stimuli. He also developed choreoathetoid movements of bilateral upper and lower limbs at 6 months of age. The child had a history of constipation since infancy which had worsened over the past week. There was no history of seizures, recurrent respiratory tract infections, or persistent vomiting. Examination

revealed microcephaly, bilateral spasticity with severe opisthotonic posturing, brisk deep tendon reflexes, bilateral upgaze palsy, positive Babinski sign, and palpable fecoliths on the abdomen. The child was diagnosed as dyskinetic cerebral palsy (CP) with SD with community-acquired pneumonia. Investigations revealed elevated creatine kinase (8573 U/L) and lactate dehydrogenase (567 U/L). Neuroimaging revealed bilateral symmetrical globus pallidus hyperintensities [Figure 1]. He was started on antipyretics, empirical antibiotics (Ampicillin and Gentamicin), and anti-dystonic drugs such as trihexyphenidyl, clonazepam, melatonin, baclofen, and midazolam infusion. His dystonia did not resolve even after 24 h after starting midazolam infusion. He was given lactulose syrup along with polyethylene glycol with which the constipation was relieved. Within the next few hours, the SD resolved. We could gradually wean the child from ventilator and make him off sedation. His biochemical parameters such as creatine kinase and lactate dehydrogenase were also normalized.

DISCUSSION

SD is characterized by frequent and severe episodes of generalized dystonia with significant morbidity and requires immediate and effective treatment. It can be either primary (DYT1) or secondary to infections, perinatal insult, trauma, or drugs.[1] Some children with genetic or acquired underlying conditions are prone to develop SD. The acquired causes such as dyskinetic CP are the most common to cause SD. Various genetic causes such as infants with ARX mutation and GNAO1-related epileptic encephalopathy can also develop SD.[1,2] Dyskinetic CP secondary to kernicterus continues to be an unfortunate but preventable occurrence in developing countries. Early markers of evolving dyskinetic CP such as upgaze palsy and rhythmic tongue thrusting need to be stressed to prevent the delay in the initiation of rehabilitation.[2-4] These early markers can help in early diagnosis and institution of early intervention before 6 months of age when surround inhibition and selective control have not yet developed and overt dystonia are not evident.[5,6] This is the probable reason for SD being a rarity in infants with evolving CP; although it may be seen in progressive neurological conditions in infancy.

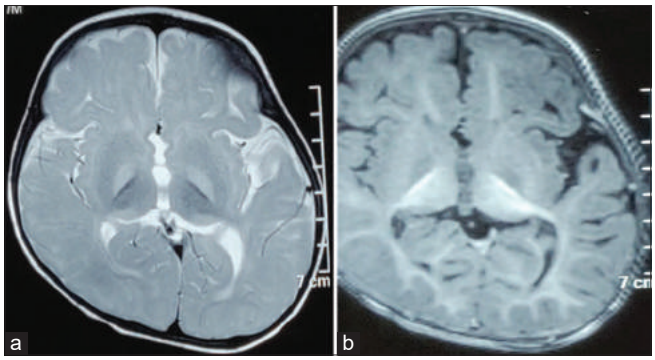

Figure 1: Neuroimaging of the index child. (a) T2-weighted image showing bilateral symmetrical globus pallidus hyperintensity (b) T1-weighted image showing bilateral globus pallidus hypointensity.

The term "prestatus dystonicus" has been proposed for an immediately preceding step in the deterioration of acute or subacute dystonia. Hence, early recognition and intervention in the pre SD step are crucial in the acute management to prevent progression to SD and its complications.[1,2] Management of SD is considerably different in infants and children when compared to adults where there are various treatment options such as anti-dystonic drugs such as trihexyphenidyl, syndopa, and tetrabenazine, sedative drugs such as benzodiazepines, deep brain stimulation, and pallidotomy.[2,3] However, in infants and children, the precipitating or trigger factors need to be addressed appropriately along with medical management. The common precipitating factors include infections (gastroenteritis with dehydration, and upper and lower respiratory tract infections), painful stimuli, constipation, poor handling of secretions, gastroesophageal reflux, chelation therapy with D-Penicillamine, zinc sulfate, and trauma.[3,4] These precipitating factors lead to a vicious cycle with worsening dystonia and this cycle can only be broken down by targeting the precipitating factors. Only running behind dystonia is not a fruitful strategy in SD. In the index child both the pneumonia and constipation precipitated SD and the dystonia resolved after treating the precipitating factors.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Authors' contribution

PM and BS: Literature review, and initial draft manuscript preparation; LS: Critical review of manuscript for important intellectual content. All authors approved the final version for publication.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Karnataka Pediatric Journal

Case Report

An unusual presentation of biotinidase deficiency in infant: High anion gap metabolic acidosis

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ABSTRACT

Biotinidase deficiency (BTD) is hereditary autosomal recessive disorder with higher morbidity and mortality if left untreated. We report this case to increase awareness about BTD, presenting with infantile seizures, encephalopathy with high anion gap metabolic acidosis, eczema and to emphasize the importance of early diagnosis in reversal of metabolic acidosis and seizures refractory to multiple anticonvulsants with biotin replacement.

Keywords: Biotinidase deficiency, Multiple carboxylase deficiency, Metabolic acidosis, Infantile seizures

INTRODUCTION

Biotinidase deficiency (BTD) is genetic disorder with autosomal recessive inheritance, in which the body is unable to recycle the vitamin biotin. BTD is of two types: Partial type in which enzyme activity is between 10 and 30% and <10% in severe form.[1,2] BTD is also known as multiple carboxylase deficiency due to deficiency of holocarboxylase synthetase (HCS) (e.g., pyruvate carboxylase) or BTD. The course of BTD can be protracted with intermittent exacerbation of chronic lactic acidosis leading to respiratory distress and other symptoms as seen in this baby. The symptoms may appear as early as 1st week following birth until up to 1 year of age. In this baby, the symptoms were noticed at around 1 month of age. Children with untreated severe BTD present with seizures, hypotonia, respiratory distress, hearing and visual deficit, ataxia, skin rashes, alopecia, and fungal infection (candidiasis). Affected children will also have developmental delay. Eczematous skin rash, alopecia, conjunctivitis, candidiasis, and ataxia are the features more specific to severe BTD. Symptoms may appear as early as 1st week following birth until up to 1 year of age. Delayed diagnosis and treatment may cause irreversible neurological damage, growth retardation, and autistic behaviors. The aim of the therapy is to increase biotin bioavailability by daily supplementation of biotin (5–20 mg) for lifetime.[3,4]

CASE REPORT

2-month-old girl born to non-consanguineously married couple, admitted to pediatric intensive care with multiple episodes of seizures since 3 weeks, breathing difficulty, conjunctivitis, eczematous skin rash in flexural areas, and hair loss [Figures 1 and 2]. Physical examination of an afebrile baby revealed tachycardia, signs of poor perfusion, altered sensorium, conjunctivitis, and deep respiratory efforts with grunting. In view of impending respiratory failure and Glasgow coma scale <8/15, child required invasive ventilation.

Investigations done showed normocytic normochromic blood picture with neutrophilic leukocytosis and thrombocytosis. Blood gas showed high anion gap metabolic acidosis, with high arterial lactates and increased levels in serum ammonia. Patient was resuscitated with fluid for shock, treated with bicarbonate correction in view of metabolic acidosis and multiple anticonvulsants. Electroencephalograph showed poorly formed background activity with right hemispheric slowing pattern, neurosonography was normal, in view of suspicion of IEM due to refractory seizures, persistent metabolic acidosis, and IEM specific medications (mitochondrial cocktail) along with antibiotics were started. Ophthalmology evaluation done showed hypermetropic silk shot fundus with refractive error and no optic atrophy. BERA showed bilateral severe to profound hearing loss [Figure 3].

Patient was suspected to have IEM possibly organic academia and BTD. TMS sent in view of suspected IEM showed BTD (enzyme activity of 25.4U against normal value 31.6–388U) and high levels of acylcanitines (methylmalonyl carnitine, and 3-OH-Isovalerayl carnitine deficiency). Urinary organic acids analyzed were within normal limits**.** Molecular analysis/genetic testing was not performed due to parental disagreement to consent for the test. Child was started on twice daily dose of oral biotin replacement (dose of 10 mg/day) along with anticonvulsants (tapered gradually over time) which showed dramatical improvement in her symptoms, that is, encephalopathy, respiratory distress, and persistent metabolic acidosis. The need for regular neuro-developmental follow-up and the risk of recurrence of symptoms in case of non-compliance to treatment has been explained to parents.

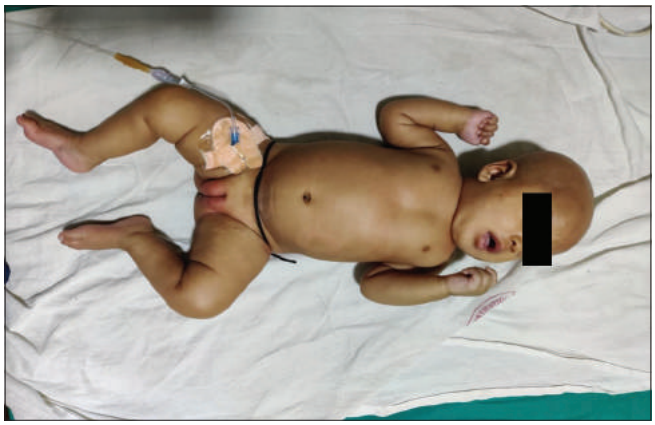

Figure 1: Two-month-baby girl presented with hypotonia, seizures, alopecia, conjunctivitis, and skin rash.

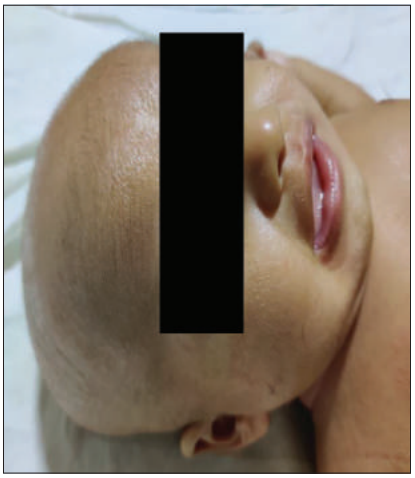

Figure 2: Baby with alopecia, conjunctivitis, and dry skin.

DISCUSSION

Biotinidase is an enzyme which acts by releasing biotin from dietary proteins. BTD is genetic disorder with autosomal recessive inheritance. Mutations of BTD gene cause BTD. The BTD gene is required for production of the enzyme-biotinidase. This enzyme recycles biotin, Vitamin B found in foods (liver, egg yolks, and milk products). Biotinidase converts dietary protein bound biotin to free (active) form. Enzymes like biotin-dependent carboxylases make use of free biotin to metabolise fats, proteins, and carbohydrates.[4] Several enzymes are impaired in BTD, the condition is named as multiple carboxylase deficiency. Impaired biotin availability causes multiple carboxylase deficiency leading to secondary ketoacidosis, hyperammonemia, and organic aciduria. Neurocutaneous symptoms such as seizures, motor

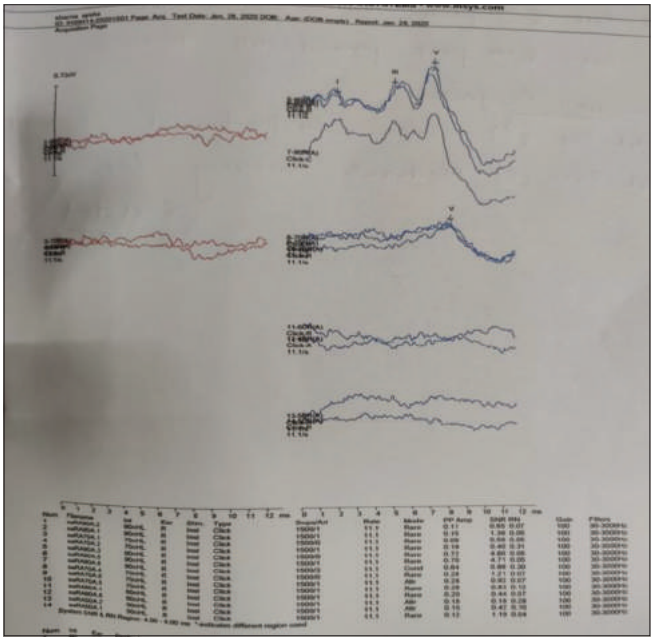

Figure 3: BERA showing right ear V peak absent till 90 Db, left ear V peak present till 70 Db.

mental retardation, spastic paraparesis, ataxia, hypotonia, sensorineural deafness, optic atrophy, eczematous dermatitis, and alopecia are associated with BTD.[5,6] Detection of low enzyme activity and genetic mutation analysis along with clinical symptoms are diagnostic.[5] The enzyme activity is <10% in severe forms whereas between 10% and 30% in partial deficiency. BTD is a mimicker of primary immunodeficiency. Urine organic acid analysis is normal or increased with 3-hydroxyisovalericacid and 3-methylcrotonylglycine. Plasma acylcarnitine analysis may show normal or increased C5-OH acylcarnitine levels. Biotin replacement may improve symptoms except hearing deficits.[6-10]

We report this case to increase awareness about BTD in setting of infantile onset seizures, encepahalopathy with high anion gap metabolic acidosis, eczema and to emphasize the importance of early diagnosis and reversal of metabolic acidosis, seizures with biotin replacement and antibiotics.

CONCLUSION

Every effort should be made in early diagnosis of biotinidase deficiency , as it is treatable and reversible .Prompt treatment with biotin supplements carries good outcome,as in our case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Karnataka Pediatric Journal

Letter to the Editor

Pediatric specialty and superspecialty training amid coronavirus disease 2019 pandemic: A thought to ponder

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Dear Editor,

Coronavirus disease 2019 (COVID-19) has disrupted the public health and the whole world is grappling with the new realities of life. Despite the acute dissident on patient care, the long-lasting bearings are not yet discernible. One of the consequences is the ongoing hindrance in the training of pediatric specialty and superspecialties in teaching hospitals. The academic curriculum of the pediatric superspecialties such as hemato-oncology, neurology, nephrology, endocrinology, and clinical immunology has been gravely impacted. This pandemic has led to an indelible modification in the learning and perception of future pediatricians and pediatric superspecialists. The conventional bedside teaching has been completely stopped as the focus of teaching hospitals has been shifted from teaching to the provision of care to the children struck by the pandemic. Clinical examinations are minimally used and the diagnosis and management primarily rely on a good history and investigations. The process of reaching a diagnosis has been completely disjointed.[1]

Academics have suffered the most. All the morning academics have been switched to online teaching in an attempt to continue medical teaching. However, a lot of residents and faculties are not interested in attending the same with most residents being tired of this format. Hence, this mode of learning is far from satisfactory as compared to physical academics.[2,3] Many of the superspecialties also acquire knowledge through specialized procedures in their specialized laboratories such as electrophysiology laboratories, endoscopy services, molecular techniques, and bronchoscopy. All these specialized procedures have greatly reduced due to the closure of outpatient services and a drastic reduction in patients visiting hospitals because of the pandemic. Even the parents avoid bringing children to tertiary care referral hospitals for tedious diagnostic exercises and non-life-threatening concerns. The evolution of telemedicine has also changed the clinical landscape minimizing the outpatient encounters.[4] However, the importance of bedside history and examination cannot be overlooked.[4] COVID-19 has altered the conduct of exit examinations for residents with clinical examination assessment being largely replaced by virtual objective structured clinical examination platforms. Besides, the COVID-19 pandemic has also adversely affected the physical and emotional well-being of the pediatric residents. A recent study revealed that nearly half of the residents suffered from symptoms of anxiety, depression, and distress.[4] Considering the endless struggles of the resident community to learn and attend to patient needs during the pandemic, the culture of professionalism and altruism needs to be redefined.[2-4]

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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