



REVIEW ARTICLE

Beyond The Usual – Infection Triggered Encephalopathy Syndromes (ITES) In Children

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ABSTRACT

Infections of the central nervous system have significant long-term morbidity and mortality in the paediatric population in both developing and developed countries. One of the dreaded presentations seen in children is that of acute febrile encephalopathy that is triggered by infectious or non-infectious agents. The COVID 19/SARS-CoV pandemic gave us newer insights into the role of immune dysregulation that is triggered by an antecedent infection. Since then, multiple new terminologies have been defined based on imaging characteristics in children presenting with acute encephalopathy. This is now collectively termed as infection triggered encephalopathy syndrome (ITES). This review looks at the expanding spectrum of infective conditions of the CNS in children and how early differentiation of the various conditions can impact the management and overall clinical outcome.

Keywords: Central nervous system, infections, artificial intelligence, MRI patterns, ITES

Abbreviations:

CNS – Central nervous system
 ITES – Infection triggered encephalopathy syndrome
 BBB – Blood brain barrier
 ADEM – Acute demyelinating encephalomyelitis
 ADS – Acute demyelinating syndrome
 ON – Optic Neuritis
 TM – Transverse myelitis
 MOG – Myelin oligodendrocyte
 NMO – Neuromyelitis optica
 ALERD – Acute leukoencephalopathy with restricted diffusion
 AESD – Acute encephalopathy with biphasic seizures and diffusion restriction
 FIRES – Fever induced refractory epilepsy syndrome
 ANEC – Acute necrotising encephalopathy of childhood
 AFCE – Acute fulminant cerebral edema
 AERRPS – Acute encephalopathy with refractory repetitive partial seizures
 MERS – Mild encephalopathy with reversible splenial lesions
 HHV – Human herpes virus
 DAI – Diffuse axonal injury
 PRES – Posterior reversible encephalopathy syndrome
 DEE – Developmental epileptic encephalopathy

Introduction

Central nervous system (CNS) infections in the paediatric population represent a significant cause of morbidity and mortality. These conditions, encompassing a spectrum from meningitis to encephalitis, present unique diagnostic, and therapeutic challenges due to the ongoing development of the paediatric brain and the diverse range of potential aetiologies¹.

The CNS, comprising of the brain and spinal cord, is protected by anatomical and physiological barriers, most notably the blood-brain barrier (BBB). This highly selective membrane restricts the passage of substances from the systemic circulation into the CNS and is crucial for maintaining homeostasis. However, the BBB can also impede the entry of immune cells and antimicrobial agents, complicating infection management. The relative immaturity of these protective mechanisms in children increases their susceptibility to a wide array of infectious agents¹.

The terminologies classically used for CNS infections include:

- Meningitis** – inflammation/infection of the meninges
- Encephalitis** – inflammation of the brain parenchyma
- Meningoencephalitis** – diffuse inflammation/infection of both the meninges as well as the brain parenchyma
- Encephalomyelitis** – involvement of the brain parenchyma and spinal cord

Encephalopathy is a state of altered sensorium resulting from disturbances in brain function. This can present as deterioration in consciousness, behavioural disturbances, difficulties in speech or higher mental functions. It can be divided into 4 categories²

- Hyperacute (seconds to minutes)
- Acute (hours to days)
- Subacute (weeks- months)
- Chronic (months – years)

Table 1: Causes of encephalopathy in children^{2,3}

	Hyperacute	Acute	Subacute	Chronic/Recurrent
Primary Neurological	1. Moderate to severe head trauma, Diffuse axonal injury (DAI) 2. Intracranial haemorrhage (Arterio-venous malformation/aneurysm) 3. Migraine	1. Infections – bacterial/Viral 2. Acute Demyelinating syndromes (ADEM, MOG antibody disease) 3. Infection triggered encephalopathy syndromes (ITES – ANE, HSES/AFCE) 3. Metabolic - Mitochondrial encephalopathy - Reye's syndrome - Urea cycle defects - Fatty acid oxidation defects 4. New onset refractory status epilepticus (NORSE) 5. Vascular – subdural haemorrhage	1. Infection triggered encephalopathy syndromes (AESD/ALERD, FIRES) 2. Infectious – Fungal, tubercular, parasitic, HIV 3. Neoplastic	1. Genetic – -RANBP2 mutation -Glycine encephalopathy -Developmental epileptic encephalopathies (DEE)

	Hyperacute	Acute	Subacute	Chronic/Recurrent
Secondary	Posterior reversible encephalopathy syndrome (PRES) – common secondary to systemic hypertension	1. Systemic infection/Sepsis 2. Hypovolemic shock 3. Adrenal crisis 4. Toxins – carbon monoxide, organo-phosphorous, opioids	1. Thyroid encephalopathy (SREAT) 2. Toxins – Heavy metal (Arsenic, Lead, Mercury)	

Unlike in infective encephalitis where there is a direct invasion of the parenchyma by pathogen, in ITES there is stimulation of the cytokine cascade in response to an infection outside the CNS. In autoimmune encephalitis, there is commonly antibody production in response to a subacute infection.

Table 2: Key differences between auto-inflammatory versus autoimmune encephalopathy⁴.

	Auto- inflammation	Auto-immune
<i>Neurological syndromes</i>	Virus associated encephalitis, neuro-vasculitis syndromes, neuro- sarcoidosis	Acute demyelinating syndromes-ADS (ADEM, TM, ON), autoimmune encephalitis (Anti-NMDAR, Anti- GAD65)
<i>Relation to infection</i>	Para-infectious	Post infectious
<i>Immune mechanism</i>	Innate immunity	Adaptive immunity
<i>Genetic syndromes</i>	Aicardi-Goutiere syndrome, RANBP2 associated recurrent ANE	Not well known
<i>Imaging</i>	May be normal in early stages, then show characteristic patterns	May be normal in autoimmune encephalitis or associated with changes in the temporal lobe- hippocampus complex In ADS, classical patterns are noted.
<i>CSF</i>	Normal or shows pleocytosis, elevated proteins	May be normal
<i>Additional investigations</i>	Elevated pro-inflammatory cytokines such as IL-6, IL-1 β , CSF neopterin, quinolinic acid	Positive antibody testing in serum (MOG/NMO), CSF (NMDAR, GAD -65), oligoclonal bands in CSF. Antibody testing may also be normal throughout or become seropositive at later stages.

Epidemiology

In children, the most common causes of encephalopathy are infectious – bacterial or viral. A systematic analysis of the burden of meningitis performed by the WHO global disease burden study 2019 noted that there were 112,000 reported deaths from meningitis in children < 5 years of age in 2019. The most common organisms across all ages were *Streptococcus pneumoniae* and *Neisseria meningitidis*⁵.

A prospective observational study in 176 Indian children found viral aetiology in 46.59% of the cohort followed by pyogenic and tubercular meningitis. Highest incidence was seen in the age group of 3-6 years with increased mortality in younger age groups (1 month-3 years). Tubercular meningitis was noted to have significant sequelae⁶.

Rickettsial infections, specifically with *Orientia tsutsugamushi*, is an important cause of acute encephalitis

in areas with dense bush vegetation, classically known as the 'tsutsugamushi triangle' (Asia, Northern Australia and islands in the Indian and Pacific Ocean). A study from Southern India found scrub typhus positive in nearly half of their study population by rapid testing although real time PCR showed positivity in only 18% of these⁷.

Both Rickettsial and arthropod borne diseases show seasonal variation with higher incidence during the monsoon seasons in Southeast Asia. Epidemics of arthropod-borne diseases with CNS manifestations include dengue encephalitis, Japanese encephalitis, chikungunya encephalitis, and cerebral malaria.

We reported a case of *Listeria* meningoencephalitis that was community acquired with rare spinal involvement implicating a dual mechanism of direct invasion as well as immune mediated injury that responded well to a combination of appropriately chosen anti-microbials and steroids⁸.

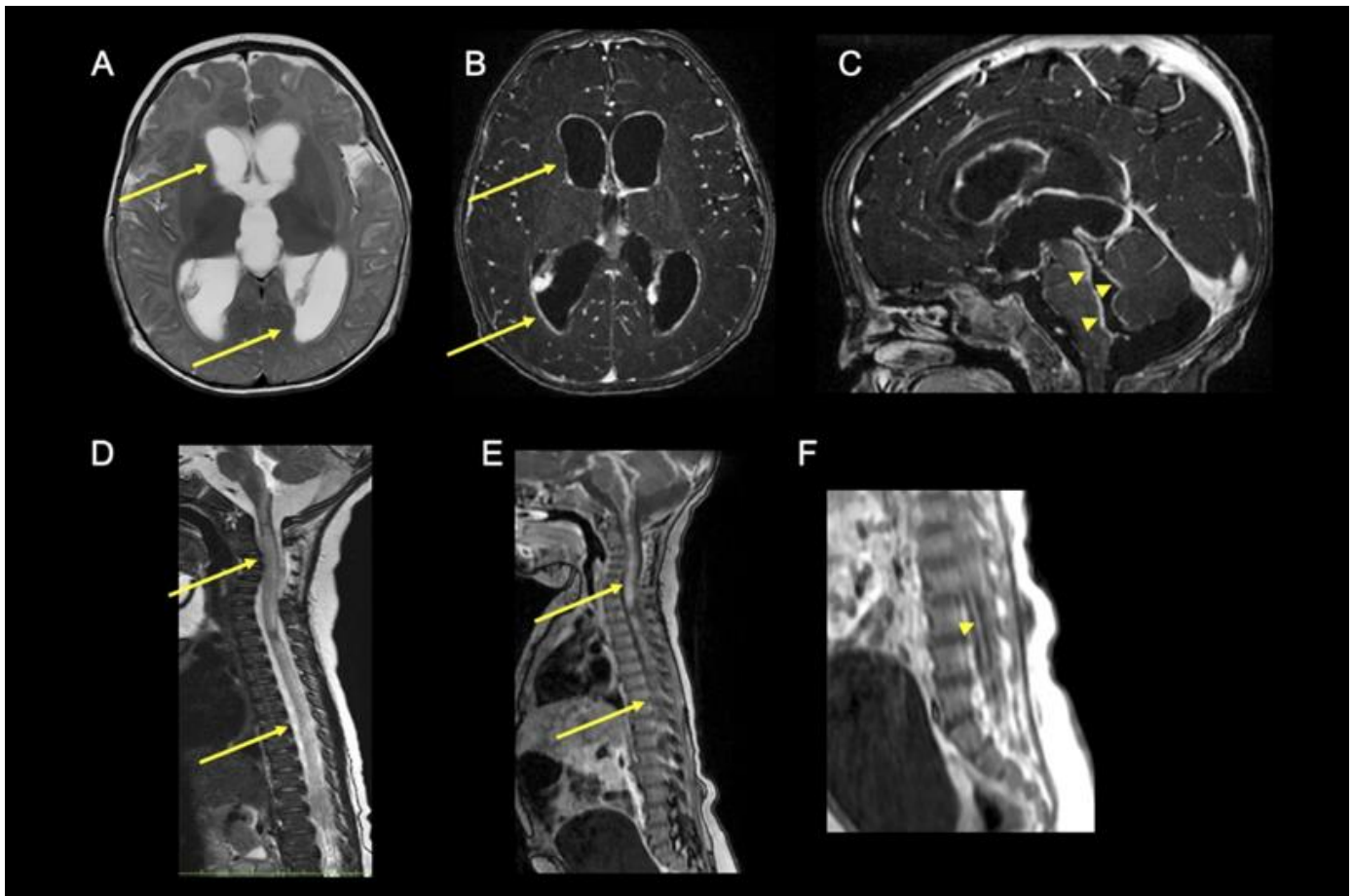


Fig. 1 (A-E): *Listeria* in a 4-month-old. Axial T2 (A) and Contrast (B,C) images demonstrate hydrocephalus (arrow) , ventriculitis (arrow) and leptomenigitis in the sulcal spaces, lining the brainstem and cerebellum (arrowhead). T2 sagittal spine (C) demonstrates long segment cord myelopathy - T2 hyperintensities. Contrast spine sagittal (D,E) depicts extensive intramedullary and cauda equina nerve root enhancement (arrows).

Herpes simplex encephalitis is the most common cause of viral encephalitis. There are several case reports and observational studies that show HSV association with autoimmune encephalitis, particularly anti-NMDAR encephalitis, although exact figures are missing. The most plausible theory behind this association suggests that direct invasion of the CNS by Herpesviridae triggers release of neuronal proteins that can induce auto-antibody production⁹.

The differentiation between the various pathophysiological mechanisms between infectious, para-infectious and autoimmune encephalitis can be difficult with significant overlap in clinical presentations and initial management strategies.

Infection triggered encephalopathy syndromes (ITES) is a recent term that denotes a group of conditions that present with rapid decline in sensorium following a febrile illness and are associated with changes on neuroimaging. These may be associated with other symptoms such as seizures or movement disorders. ITES as an entity is different from other autoimmune or post infectious conditions such as autoimmune encephalitis and acute demyelinating encephalomyelitis (ADEM).

The International Consensus definitions for ITES by Sakuma et al published in August 2024 highlighted the

various conditions that encompass this term and the pathophysiological mechanisms that differentiate the ITES group from other conditions¹⁰. ITES comprises five conditions that are based on the MRI findings.

1. Acute encephalopathy with biphasic seizures and restricted diffusion (AESRD)
2. Acute necrotising encephalopathy (ANEC)
3. Acute fulminant cerebral edema (AFCE)
4. Acute shock with encephalopathy and multi-organ failure (ASEM)
5. Mild encephalopathy with reversible splenic lesion (MERS)

Acute encephalopathy with biphasic seizures and restricted diffusion (AESRD/AESD) is the most common para-infectious encephalopathy in children. It commonly follows infection with pathogens such as influenza A, rhinovirus, mycoplasma and HHV 6. The average age group of children is around 9 months -2 years which is younger than those with FIRES. It usually presents with prolonged febrile seizures lasting >30 mins followed by a period of normal consciousness and then a decline in sensorium. This is followed by complex partial seizures on day 4-6 of illness. The initial MRI may be normal but later images can show characteristic pattern of restricted diffusion or atrophy. The diagnostic criteria is as below¹¹:

Diagnosis of AESRD is made if essential plus any of the additional criteria are present

A) Essential

1. Occurs during the course of a febrile illness
2. Onset is characterised by prolonged febrile seizures lasting >30 mins in the first 2 days of illness

B) Additional

3. Secondary seizures (usually cluster of complex partial seizures) or alteration in level of consciousness on Day 3-7 of illness
4. DWI shows high signal in the subcortical white matter (bright tree appearance) and/or in the cortex at day 3 to 14. Sparing of pre- and postcentral gyrus (central sparing) is usually observed.
5. After 2 weeks, residual lesions or atrophy on CT/MRI, or decreased blood flow on SPECT are observed in the frontal or fronto-parietal region, often with central sparing

Acute necrotising encephalopathy of childhood (ANE/ ANEC) is a rare but devastating condition following viral infection. Although, the most implicated organisms are influenza A and HHV 6, dengue is a known cause in the Indian subcontinent. Dengue associated necrotising encephalitis (DANE) affects similar areas as those in classical ANE and is now considered a variant of

sporadic ANE. In contrast to AESD, there is a rapid deterioration of sensorium at onset (within a few hours). Seizures and encephalopathy are the most common presentation; movement disorders occur as sequelae of the disease¹². The diagnostic criteria for ANEC given is as follows ¹¹;

1. Acute encephalopathy related to a febrile viral infection: rapid reduction in consciousness and seizures
2. CSF examination shows normal counts and increased proteins
3. Symmetrical and multiple brain lesions on CT/MRI. These include bilateral thalamic lesions (most common) and lesions in periventricular areas, putamen, upper brainstem tegmentum, and cerebellum
4. Elevated transaminase level with no elevation in serum ammonia levels
5. Exclusion of other diseases such as severe viral/bacterial infections, metabolic conditions – mitochondrial disorders (Leigh's), Reye's syndrome, Wernicke encephalopathy, carbon monoxide poisoning, methylmalonic acidemia; hypoxic brain injury, vasculitis.

Genetic predisposition is seen in children with missense RANBP2 mutations (ANE 1). RAN binding protein 2 (RANBP2) is a key component in the nuclear pore complex (NPC) and has various functions that include intracellular signalling and mitochondrial trafficking. Mutations in this, cause dysregulation of mitochondrial function and disruption of the blood brain barrier allowing cytokines to cause injury. The presentation is with single or multiple episodes of ANEC with or without an infective trigger and may be confused with ADEM or Leigh's disease for the uninitiated physician. Sequelae are noted in the form of dystonia, seizures and cognitive issues that tend to persist or worsen with repeated episodes. Unlike sporadic ANE, transaminitis and coagulation disturbances are usually not associated with ANE¹³.

Mild encephalopathy with reversible splenial lesion (MERS)

is the least severe form of ITES as the name suggests and is characterised by alteration in sensorium during a febrile illness for 1-2 days followed by improvement to baseline GCS without any long-term sequelae. During the acute phase, the imaging shows reversible lesion in the brain with restricted diffusion. Based on imaging findings, there are 2 types of MERS – Type 1 has only splenial involvement and Type 2 and splenial plus symmetric deep white matter lesions.

Familial or recurrent MERS is seen with Type 2 lesions and are associated with functional defects in MYRF gene¹⁴. MYRF regulates oligodendrocyte differentiation and maintenance of myelin integrity. Therefore, defects result in encephalopathy with vacuolisation. The transient diffusion restriction seen in MERS is postulated to result from intramyelinic oedema.

Essential

1. Onset of neurological symptoms after a febrile illness
2. Neurological manifestations – altered sensorium, reduced level of consciousness, personality change >24 hours
3. MRI lesion in splenium of corpus callosum with restricted diffusion
4. Exclusion of other diseases – acquired demyelinating syndromes, RESLES – reversible splenial lesion syndrome seen with anti-seizure medication, hyponatremia, hypoglycemia, high altitude induced cerebral oedema, etc.

Common

1. Other clinical symptoms such as seizures/hallucination
2. Spontaneous recovery with a self-limited illness course
3. MRI involvement of corpus callosum, periventricular white matter and other areas of the cortex

Acute shock with encephalopathy and multi-organ failure (ASEM)/Acute fulminant cerebral edema- Both these conditions represent a continuum of hyperacute conditions under the term ITES. ASES was previously known as HSES (haemorrhagic shock with encephalopathy syndrome). AESM presents with high grade fever, haemorrhage, disseminated intravascular coagulation followed by a rapid onset of encephalopathy/coma and decline in renal functions. AFCE shows similar radiological findings as ASEM but without features of haemorrhage or coagulopathy.

There are two other related conditions that are currently classified under epilepsy syndromes but possibly share similar pathophysiological mechanisms – Fever induced refractory epilepsy syndrome (FIRES) and hemiconvulsion-hemiplegia epilepsy syndrome (HHE). These usually show normal imaging in the early stages and atrophy in later stages.

Diagnosis

The diagnosis of CNS infections requires timely and appropriate samples. Classically, cerebro-spinal fluid (CSF) is collected from L1-L2 space in children and tested for biochemical, cellular and microbiological parameters using various methods such as gram staining and culture. If blockage is suspected due to lack of CSF flow during lumbar puncture and the child is less than 2 years of age with an open anterior fontanelle, samples can be collected by an expert by placing the needle directly into the lateral ventricles. Other samples that can be collected include pus for intracranial abscess or tissue from suspected infectious lesion (for eg-fungal). This requires the expertise of a neurosurgeon.

Although, CSF sample remains the 1st line diagnostic test especially in resource poor settings, the results depend on the timing and quality of the sample and the expertise of the laboratory specialist. The results are also modified by the concurrent use of anti-microbial agents making detection of pathogens difficult.

Current methods for pathogen detection have improved the yield with shorter turnaround times (TAT). These include pathogen specific PCR (eg HSV 1 and 2 PCR) as well as multi-panel PCR which can detect pathogens even when the CSF cultures are negative.

One such example was our case report on community acquired *Listeria meningitis* in a 4-month-old female child. Routine CSF study showed neutrophilic leucocytosis with high protein, but culture was sterile. *Listeria monocytogenes* was detected in the multiplex PCR panel (BIOFIRE®) within 6 hours of sample collection and the child improved on appropriate antibiotics (High dose Ampicillin and single dose of Gentamycin)⁸.

The Paediatric Infections point of care (PI-POC) trial compared the utility of several diagnostic tools that would increase the yield of pathogen detection in low resource settings (Uganda). These included novel DNA based diagnostic assay, multiplex PCR based meningoencephalitis panel, proteomics profiling from blood

samples of cases and myxovirus resistance protein A (MxA) as a biomarker for viral CNS infections¹⁵. This group found commercially available multiplex PCR kits to be useful in detecting bacterial pathogens at quicker turnaround time, thus helping in appropriate management and shortening duration of hospital stay¹⁶.

O'Brien et al reported that the multiplex PCR panels had 93.8% sensitivity and 90% specificity as compared to microbiological culture in detecting organisms causing paediatric CNS infections with a reduction in detection time from 6 days to 2 days and duration of hospital stay from 5 days to 3 days¹⁷.

Metagenomic next generation testing (mNGS) is the latest in the diagnostic armamentarium of childhood CNS infections with high throughput, sensitivity and low risk of bias. It can be done either on a whole cell DNA or a cell free DNA specimen. Studies on paediatric patients have shown the mNGS significantly increases the detection rate of pathogens that are difficult to be picked up by conventional methods such as *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Nocardia* etc¹⁸. Cell free DNA mNGS appeared to have higher detection rates for viral pathogens and tuberculosis as compared to whole cell DNA if done 1-6 days after starting anti-microbial therapy and correlated with the clinical picture in >67.5% of the cases^{19,20}.

As mentioned earlier the differentiation between infective, para-infectious and autoimmune aetiologies, especially in the early stages is nearly impossible due to similarities in the clinical presentation. Opportunity to target the exact aetiology may be missed unless there are reliable clinical and diagnostic parameters to predict the evolution and manage them appropriately.

Uematsu et al looked at predictors for AES in children presenting with prolonged febrile status. They developed a simple scoring system based on laboratory parameters which included an elevated creatinine, hyperglycemia (RBS>200mg/dl) and elevated AST²¹.

Tada et al devised a similar predictive scoring system that included the GCS level at admission, duration of seizures, age of patient, mechanical ventilation and laboratory parameters (Creatinine, AST and blood glucose)²². A score of more than 4 was suggestive of AES. The elevation in creatinine levels which was common in both the above studies was attributed to the increased energy consumption due to prolonged seizures with leakage of creatinine through damaged blood brain barrier. Both the studies did not report abnormal renal function in any of the patients.

Serum hyponatremia is often seen in MERS. Serum sodium levels were significantly lower in MERS patients as compared to age matched controls in a study by Takanashi et al in 2009. Whether the systemic hyponatremia directly causes or partly contributes to the intra-myelin oedema seen in MERS is still not well understood. The authors also found it difficult to differentiate MERS from hyponatremic encephalopathy²³.

Monitoring the level of cytokines in CSF is helpful for administering targeted treatment. Tomioka et al noted that cytokine levels peaked within 12-24 hours of onset of encephalitis symptoms and pro-inflammatory cytokines (IL-1 β , IL-6) reached baseline levels by 48 hours. The levels were higher in those with Haemorrhagic shock encephalopathy syndrome (HSES) and AESRD as compared to those with febrile seizures²⁴.

Dale et al compared CSF neurotransmitters in children with ITES vs those with acute encephalitis. They measured CSF neopterin, quinolic acid, kynurenine and kynurenine/tryptophan ratio using a combination of liquid chromatography and tandem mass spectrometry. The results were available in 4 hours and an elevated CSF neopterin level significantly favoured ITES over acute encephalitis. This is particularly helpful as imaging may be normal in the early stages, especially in FIRES and initiating early treatment has shown better outcomes across several studies²⁵.

Imaging

The role of neuroimaging in paediatric CNS infections is pivotal and crucial. It helps to detect and differentiate

various infections, identify complications and helps in guiding treatment. MRI brain is the preferred modality. Contrast enhanced and diffusion weighted images are used to help differentiate infective conditions from other causes such as metabolic or demyelinating conditions. MR spectroscopy is used to differentiate infective masses from tumours²⁶.

In the subcontinent, tubercular meningitis continues to be the most common CNS infection after viral encephalitis. The radiological features like the clinical findings are varied and often mimic other conditions. MRI brain with contrast is the preferred technique as non-contrast scans may miss the diagnosis in paucibacillary infection. Classically, exudates in the basal cisterns and near the optic chiasma are noted. Complications such as hydrocephalus, infarcts, vasculitis and cranial nerve involvement may be noted. Single tuberculomas are often difficult to differentiate from neuro-cysticercosis. Diffusion weighted imaging shows diffusion restriction in tuberculomas and spectroscopy may help to differentiate in the absence of scolex or other classical features – tuberculomas show lipid-lactate peaks due to areas of necrosis while neuro-cysticercosis shows amino acid peaks²⁷

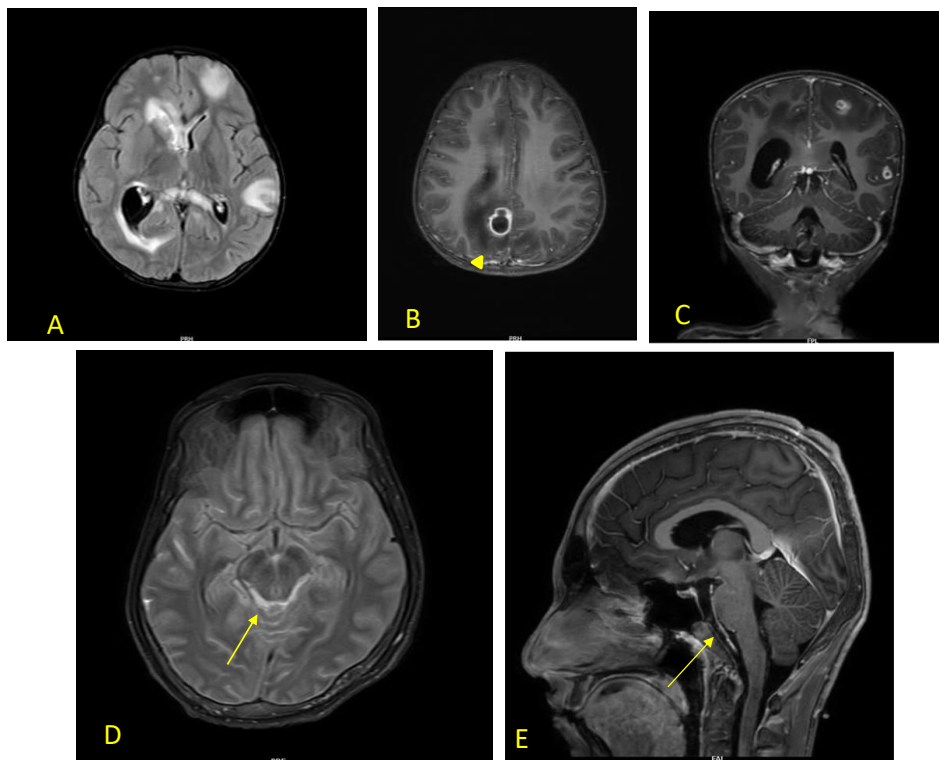


FIG 2 A-E: CNS TUBERCULOSIS- A,C : 4-year-old with thalamic and cortical with multiple ring enhancing lesion with ventriculitis, B: tubercular abscess (arrowhead) with perilesional oedema and mild midline shift. D,E – 14-year-old with TBM showing basal exudates (arrows)

The diagnosis of ITES is based on the imaging findings in addition to the clinical features. MRI is preferred over CT brain. Diffusion weighted imaging and FLAIR sequences are key modalities in the imaging protocol.

In AESD, there is a biphasic pattern of illness which correlates with radiological evolution. The initial scans

are usually normal followed by diffuse restriction of the frontal or fronto-parietal subcortical white matter with central sparing. Later scans show cerebral atrophy. Based on the imaging findings, Kamate et al suggested a change of the terminology to ALERD (Acute Leukoencephalopathy with restricted diffusion) as it depicts the condition better²⁸.

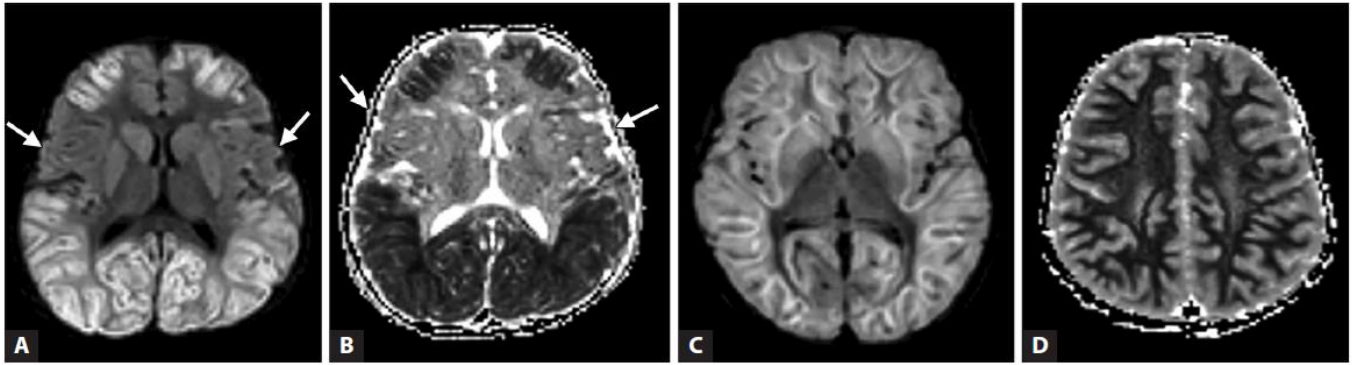


FIG 3. (A-D) Acute Leukoencephalopathy with restricted diffusion (ALERD)- Axial brain MRI demonstrating restricted diffusion – cytotoxic oedema on DWI (A) and corresponding low signals on ADC (B) in bilateral cerebral hemispheres, with sparing of the central perisylvian regions (arrows). Axial brain MRI showing diffuse restricted diffusion – cytotoxic oedema on DWI (C) and corresponding low signals (D) in the bilateral cerebral hemispheres. (Image courtesy – Dr Nihal Reddy, Consultant Neuro-radiologist, Hyderabad)

In ANEC/ANE1, there is involvement of bilateral thalami in the form of areas of diffusion restriction with haemorrhagic necrosis ('trilaminar sign'). Involvement of midbrain, brainstem and cortex are also noted and have

been associated with poorer outcomes. In milder forms of sporadic ANE, spontaneous resolution of lesions with residual hemosiderin deposits are noted with minimal sequelae.

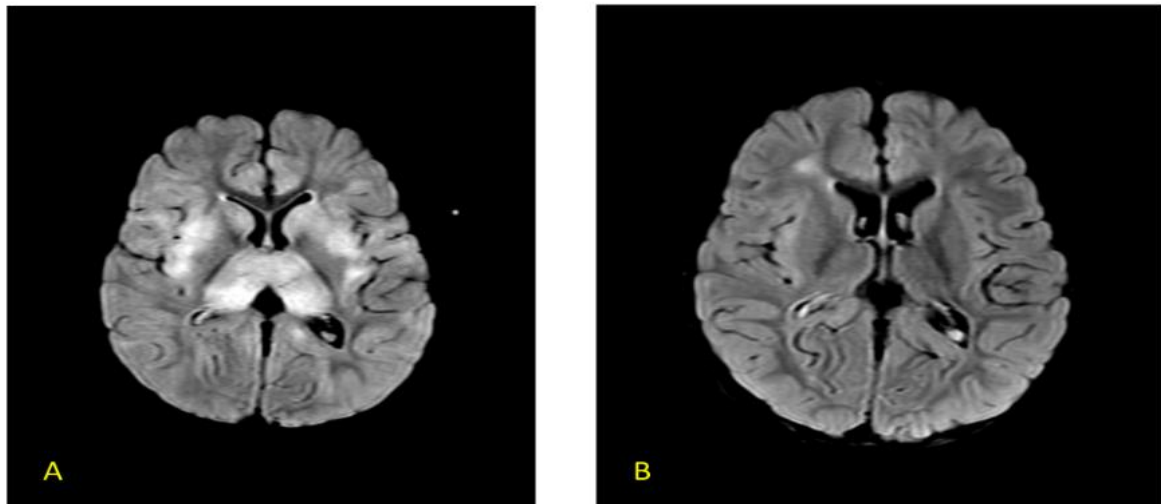


FIG 4: 9-month-old boy with rapid decline in sensorium following viral upper respiratory tract illness. He tested positive for Influenza A on nasal swab PCR. Scan was done within 12 hours of presentation and showed early changes of ANEC. T2 FLAIR sequence on admission showing diffuse edema in bilateral thalami and lentiform nucleus with diffusion restriction; B – repeat scan 6 weeks later shows near complete resolution of lesions with good clinical recovery.

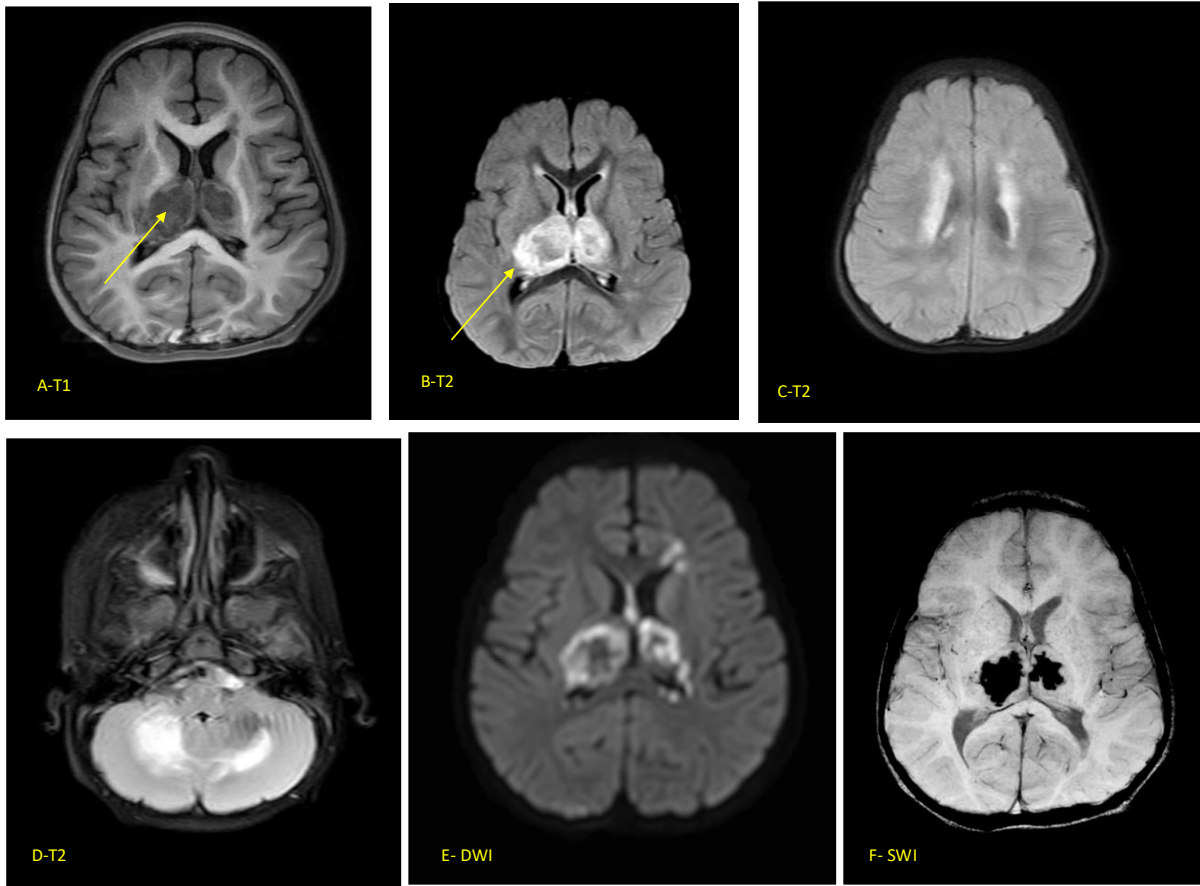


Fig 5 (A-F) – Acute necrotising encephalopathy of childhood (ANEC) in a 12-month-old child with viral gastroenteritis 2 days prior to rapid decline in sensorium. Classical ‘Trilaminar’ sign (arrow) noted in the T1 (A) and T2 (B-D) axial images in bilateral thalamic, hyperintensities also present in cerebellum and periventricular regions with restricted diffusion on DWI (E) and blooming on SWI (F) (s/o micro-haemorrhages). MR spectroscopy did not show inverted lactate doublet. FIRES is usually associated with normal imaging at the outset. Some cases show swelling in the mesial temporal or hippocampal regions presumably from prolonged seizure activity. Late scans show diffuse cortical atrophy due to a combination of brain injury and use of prolonged steroids.

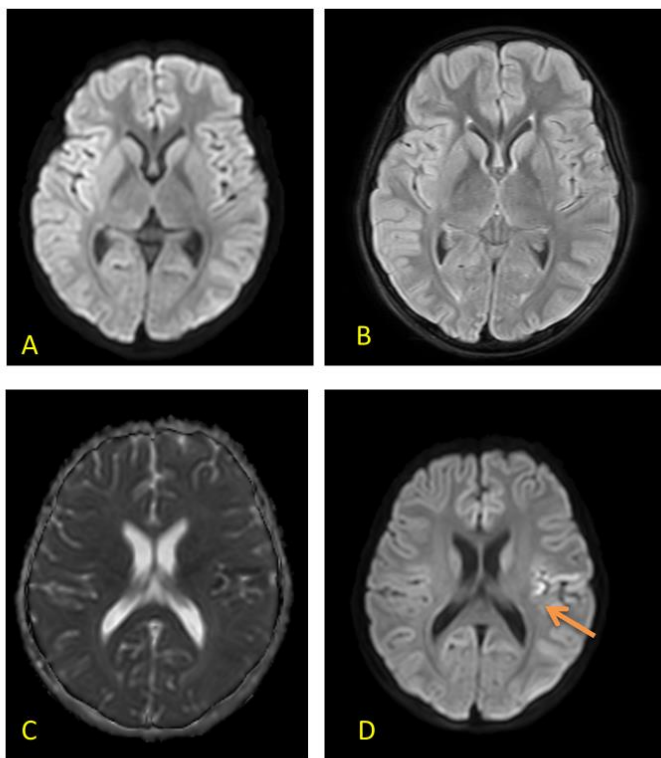


FIG 6 A-D: Fever induced refractory epilepsy syndrome (FIRES)- 8-year-old with onset of refractory seizures on Day 7 of febrile illness. Initial MRI (T2/FLAIR) images are normal (A,B). Subsequent scan done 10 days later showed diffusion restriction in left peri-Rolandic area - arrow (C,D). EEG – showed persistent electrical seizures in left >right occipital regions which responded well to Midazolam and Ketamine infusion along with ketogenic diet.

MERS is characterised by reversible splenic lesions predominantly and a milder course with minimal sequelae as compared to the other ITES. DWI sequences on MRI help to identify lesions with homogenous reduction in diffusion in the corpus callosum or at least the splenium without any contrast enhancement. Those with MERS

secondary to rotavirus encephalitis may progress to develop Cerebellitis and cerebellar atrophy in later stages. Takanashi et al also reported that MERS type 2 lesions tend to resolve to MERS 1 in the initial 1-2 days before complete resolution by day 7 of illness²⁹.

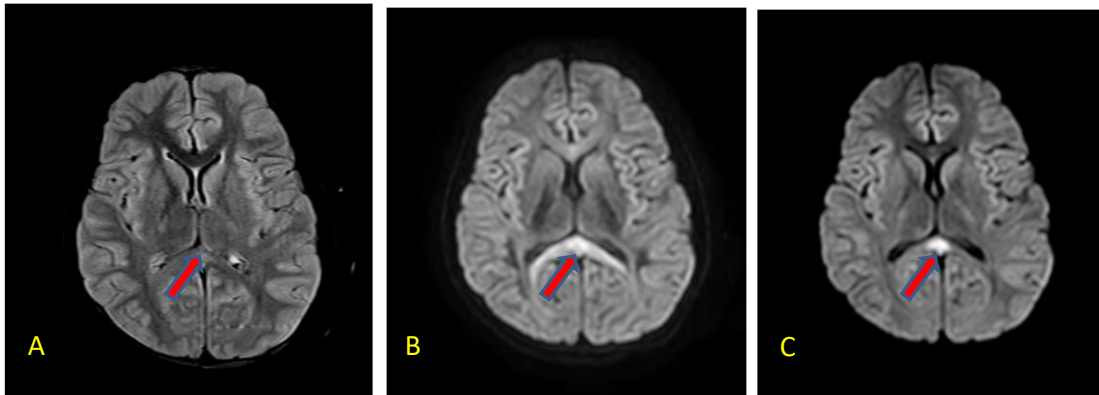


FIG 7 A-C Mild encephalopathy with restriction in splenium (MERS). 12 year old girl with fever triggered seizures followed by rapid decline in sensorium (GCS 9/15) requiring mechanical ventilation for 48 hours. Serum sodium levels at presentation was 131 mg/dl. Recovery to baseline on Day 4 of illness with no neurological sequelae at discharge. MRI brain with T2 FLAIR (A) and DWI sequences (B,C) on Day 1 of illness show corpus callosum involvement, mainly splenium with diffusion restriction. Chikungunya PCR positive.

AFCE and AEM/HSES represent severe end of the spectrum of ITES, characterised by life threatening hyperacute onset of cerebral oedema or multi-organ dysfunction respectively. They carry a high mortality rate

of about 80%. Both the entities have similar clinical presentations and radiological findings and probably are a part of the same severe neuro-inflammatory process.

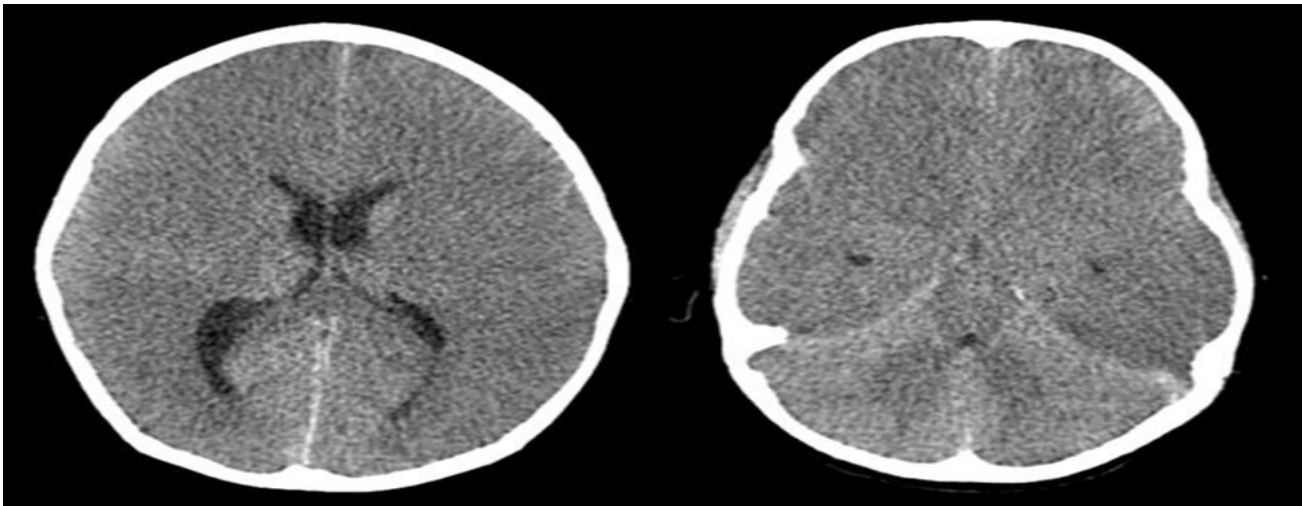


FIG 8 (A-B) Axial CT scan in a 7-year-old with AFCE showing diffuse cerebral edema (A) with 'white' cerebellum sign (reversal) (B) – prognosis is very poor in this case (Image courtesy - Dr Nihal Reddy, Consultant Neuro-radiologist, Hyderabad)

Treatment

The initial management of a child with suspected CNS infection is stabilisation. This includes taking care of airway, breathing and circulation primarily and to rule out features of raised intracranial pressure/ impending brainstem herniation as children often decompensate rapidly.

General neuroprotective measures such as maintaining normotension, normoglycemia and normothermia is essential. 20% Mannitol/3% saline is commonly used to

reduce intracranial hypertension. Both have been shown to be equally efficacious in adult studies. In children, however, hypertonic saline (HTS) is preferred due to ease of administration and better safety profile.

A prospective study comparing hypertonic saline with 20% mannitol in 57 children with acute CNS infection reported better fall in intracranial pressure (ICP) and improvement in cerebral perfusion pressure (CPP) with hypertonic saline³⁰. Shein et al looked at real time data using invasive intracranial monitoring device to look at

the effectiveness of various pharmacological agents to reduce raised intracranial pressure and found HTS to be most effective in acute reduction in raised ICP when compared to phenobarbitone, fentanyl and mannitol³¹.

The use of antimicrobial treatment in paediatric CNS infections is guided by the epidemiology of pathogens in that geographical region and seasonal variation. The protocol may differ from unit to unit. In acute encephalopathy, a combination of antibiotic (usually ceftriaxone) and anti-viral (acyclovir/oseltamivir) is used. Azithromycin or doxycycline is used in cases of atypical organisms such as rickettsia. Anti-malarial agents are used if the child is positive for *P. Vivax* or *P. falciparum* on the blood smear or antigen test.

Treatment in ITES

In ITES, the treatment is based on the understanding of the pattern of cytokine activation and targeted therapy is recommended.

IMMUNOMODULATORY AGENTS:

Steroids form the first line of immunomodulation in ITES due to ease in availability, administration and pricing. High dose of methylprednisolone 30mg/kg/dose or intravenous dexamethasone is given over 3-5 days. In the subcontinent, care must be taken to rule out subclinical tuberculosis prior to initiating steroids. Several studies reported better outcomes when steroids are given in the first 24 hours of presentation.

Horino et al studied the outcomes of **intrathecal dexamethasone (IT-DEX)** in 6 children with FIRES after the first week of illness onset. This is based on the theory that FIRES is a neuro-inflammatory condition with increased levels of pro-inflammatory cytokines in CSF than in serum. All patients could be weaned off sedation and ventilation by approximately day 5 of IT – DEX with reduced duration of ICU stay and improved seizure control³².

Intravenous immunoglobulin (Ivlg) is the 2nd most common agent used for immunomodulation in ITES. It suppresses cell activation and cytokine production. In ANE, a combination of steroids and Ivlg has been shown to reduce mortality. The outcomes in the group treated with Ivlg were better as compared to placebo. However, the efficacy of Ivlg in acute encephalitis is still debatable³³.

Tocilizumab is an anti-interleukin 6 (IL-6) receptor monoclonal antibody that has shown promising results in children with ANE. It has also been shown to help in repairing the blood brain barrier and thereby limiting the entry of pro-inflammatory cytokines. It can be given as a single dose of 8-12 mg/kg or in 2 doses 12 hours apart. It is believed that early dosing has better outcome but there is a lack of consensus regarding the timing and dosing of Tocilizumab in ANE. The outcomes are better when Tocilizumab is used along with Ivlg and intravenous steroids.

Lee et al reported the beneficial role of Tocilizumab in Rituximab-refractory autoimmune encephalitis one month after treatment with 1st line immunomodulation

(steroids and Ivlg) and standard Rituximab regimen (375mg/m²). The Tocilizumab group had better modified Rankin scores (mRS) compared to those treated with repeated doses of Rituximab. The delayed role of tocilizumab may be related to blocking the action of IL-6 in B and T cell differentiation and proliferation³⁴.

Anakinra is an interleukin 1 antagonist that has been tried mainly in FIRES/AERPS. In a case series of 25 patients with FIRES across an international population, early use of Anakinra (Median = 20 days) showed reduction in seizure burden, shorter duration of ventilation and ICU stay but didn't necessarily improve the final outcome. Anakinra is started at a dose of 3-6mg/kg/day (max 10mg/kg/day) and continued for a duration of 12-24 months³⁵. Some case studies have also reported the beneficial role of Anakinra and Tocilizumab in the chronic phase of FIRES³⁶.

OTHER THERAPIES

Targeted therapeutic hypothermia (TTM) differs from head cooling that is done in neonates for hypoxic ischaemic encephalopathy (HIE) in that the whole body is moderately cooled to maintain temperature of 34.5-37-degree centigrade as compared to brain hypothermia therapy where the temperatures range from 32-34 -degree centigrade³⁷.

Hypothermia has been a known therapeutic option for many years in the adult cardiac and trauma ICUs. In children, except neonates, therapeutic hypothermia is not routinely administered and there is a lack of protocol for using TTM in Paediatric ICUs.

TTM acts by lowering the body temperature, lowering the brain basal metabolic rate and therefore reducing the cytokine mediated injury. It is used as an adjunctive treatment in children with AESD or FIRES in addition to other anti-seizure medications. A combination of head cooling (BHT) in the acute phase (72 hours) followed by TTM for 96 hours showed reduction in seizure recurrence on rewarming. No neurological sequelae was detected for the child at discharge on day 28³⁸.

Other therapies – drugs such as Dextromethorphan (an anti-NMDAR antagonist) have been tried in a few cases with refractory seizures and was associated with better seizure control, mitochondrial cocktail drugs such as thiamine, biotin, CoQ10, pyridoxine, vitamin E etc may show reduced seizure occurrence in acute encephalopathy. Pyridoxine is beneficial in refractory seizures as it acts as a coenzyme to GAD (glutamic acid decarboxylase) receptors

Early ketogenic diet and steroids have been shown to have benefit in FIRES in a review by Kessi et al. All other therapies did not show any significant values in the study³⁹.

Scope for future research

ITES and other immune mediated conditions in the paediatric age is still in its incipient stages but has tremendous potential in terms of early prevention of

devastating sequelae if picked up early. Most of the breakthrough research in these conditions have come from the dedicated group of paediatric neurology teams in pockets across the globe (Japan, Australia, United Kingdom). More data is required from other high burden countries such as India to understand the effect of geographical and ethnic factors. It is also important to look into economical therapeutic options especially in developing nations where financial constraints, logistics (drug availability, healthcare access) and delays in referral play an important role in deciding treatment.

Machine learning/Artificial intelligence in medicine is picking up a lot of steam in recent years. Its use in paediatric neurology has expanded to aid in tumour

diagnosis, neonatal seizure detection and in autism spectrum disorder⁴⁰⁻⁴⁴. It could prove beneficial in collating all the clinical and imaging data in ITES to create algorithms for quicker diagnosis and appropriate management for doctors practicing in peripheral areas.

Conclusion

This short article highlights the expanding spectrum of Paediatric CNS infections and the immunological mechanisms that are at play in the causation of ITES group of disorders. Early recognition with clinical, basic laboratory and radiological parameters can help in diagnosis and appropriate management.

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