Fever, Seizures and Encephalopathy: From Bush Fires to Firestorms

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Abstract

Fever-associated seizures and febrile encephalopathy are common neurological problems in children. Infections of the nervous system are responsible for the majority of cases. However, there is a spectrum of infection-associated and inflammatory conditions associated with the triad of fever, seizures, and encephalopathy. Apart from complex febrile seizures and febrile status epilepticus, fever infection-related epilepsy syndrome of childhood (FIRES), infantile hemiconvulsion hemiplegia epilepsy syndrome (IHHE), acute encephalopathy with delayed diffusion restriction (AESD), acute necrotizing encephalopathy of childhood (ANE), and reversible splenial lesion syndrome (RESLES) are age-related clinical phenotypes of fever-related epilepsy and encephalopathy. Awareness of these entities is important for appropriate diagnosis and the prompt use of immunomodulatory/immunosuppressive therapies. In this review, we discuss the pathophysiology, clinical phenotypes, and management approaches of these fever-related seizure and encephalopathy states.

Keywords: Acute encephalopathy with delayed diffusion restriction (AESD), acute encephalopathy with repetitive refractory partial seizures (AERRPS), acute necrotizing encephalopathy of childhood (ANE), devastating epileptic encephalopathy in school-aged children (DESC), encephalopathy, epilepsy, febrile seizures, febrile status epilepticus, fever, fever infection-related epilepsy syndrome of childhood (FIRES), infantile hemiconvulsion hemiplegia epilepsy syndrome (IHHE), reversible splenial lesion syndrome (RESLES)

Introduction

Seizures associated with fever are common in children. Febrile seizures are probably the most commonly encountered acute neurological condition in children, with benign outcomes in the majority.[1] The spectrum of fever-related seizures ranges from simple and complex febrile seizures to febrile status epilepticus, genetic epilepsy with febrile seizure plus, and Dravet syndrome. In addition to these predominantly genetically determined entities, other fever-associated epilepsy and encephalopathy disorders include fever-infection-related epilepsy syndrome (FIRES), devastating epileptic encephalopathy in school-aged children (DESC), new-onset refractory status epilepticus (NORSE), acute encephalopathy with repetitive refractory partial seizures (AERRPS), idiopathic hemiplegia hemiconvulsion syndrome (IHHE), and acute encephalopathy with delayed diffusion restriction (AESD). Disorders that are characterized by fever and encephalopathy but infrequent seizures include acute necrotizing encephalopathy (ANE), mild encephalopathy with reversible splenial lesions (MERS), and acute demyelinating encephalomyelitis (ADEM). The complex interplay of fever, brain immaturity, and infection-triggered immune and inflammatory mechanisms seems to create a setting for this group of disorders [Figure 1]. In this review, we discuss the clinical features, possible underlying pathophysiological mechanisms, and treatment options for childhood neurological disorders associated with fever, seizures, and encephalopathy [Table 1].

Fever and the Nervous System's Susceptibility to Seizures

Fever increases neuronal excitability, especially in the hippocampus. At higher body temperatures, alteration of membrane properties of pyramidal cells and interneurons in the hippocampus occurs.[2] Many physiological events, including resting neuronal membrane excitability, synaptic transmission, and endo- and exocytosis, are affected by hyperthermia.[3] L-type calcium channels have been found to be hyperpolarization-activated and become intrinsically active at temperatures >37°C.[4] It has also been postulated that hyperthermia induces glutamatergic excitatory inputs through N-methyl-D-aspartate receptor (NMDAR) and transient

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receptor potential vallinoid-4 (TRPV-4), resulting in a net neuro-excitatory state.[5-7]

Fever, either by itself or by virtue of the associated infection, incites an inflammatory response in the brain. IL-1β, a potent pyrogen, has been extensively studied for its putative role in the pathogenesis of febrile seizures. It induces hyperthermia, NMDA-induced intracellular calcium influx,[8] and glutamate-mediated hyperexcitability[9] and thus potentiates seizure generation.[9,10] IL-1-receptor and NMDAR are co-localized on hippocampal dendrites, with possible enhanced crosstalk.[8,10] Additionally, the IL-1β allele 511*2, which confers enhanced IL-1β production, has been found in higher frequency in children with FS and in adults with temporal lobe epilepsy.[11] In a recent Korean study, significantly elevated post-ictal levels of IL-1β, IL-6, and HMGB1 (high-mobility group box 1) were found in children with FS. In the same study, gene variants at IL-1β*31 and IL-1β *511 promoter regions correlated with higher post-ictal IL-1β levels, suggesting that few genetic variants predispose to increases inflammatory cytokines after febrile seizures.[12] Tumor necrosis factor-α (TNF-α) also amplifies glutamate-mediated AMPA response and increases $GABA_A$ receptor endocytosis, contributing to hyperexcitability. 9 Hyperthermia-induced hyperventilation and subsequent respiratory alkalosis has also been postulated to contribute to seizure generation, but this has not been proven [Figure 2].[13]

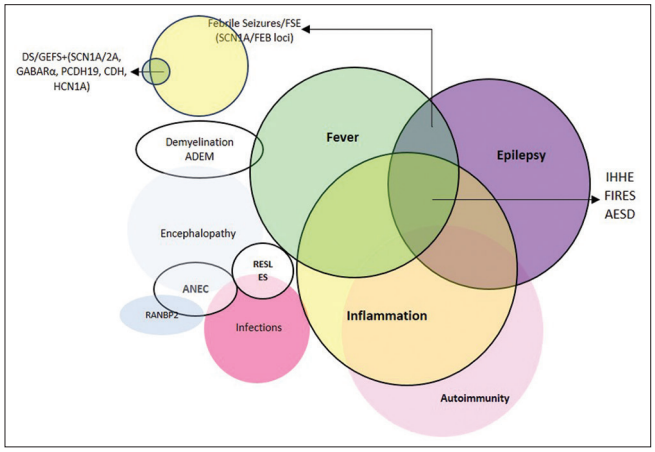

Figure 1: Venn diagram depicting the overlap between epilepsy, fever, inflammation, autoimmunity, infections, genetics, and related clinical conditions. Abbreviations: CDH2: Cathedrin-2, DS: Dravet syndrome, GABARα: gamma-aminobutyric acid receptor, GEFS: genetic epilepsy with febrile seizure, HCN1A: hyperpolarization-activated cyclic-nucleotide gated channel, HMGB1: high-mobility group box 1, IEMS: Inborn errors of metabolism, IHHE: infantile hemiconvulsion hemiplegia epilepsy syndrome, LPS: lipopolysaccharide, PCDH19-protocathedrin 19, POLG: polymerase gamma, SCN: voltage-gated sodium channel, TNFα: tumor necrosis factorα

These responses are further modified by individual genetic factors. Pathogenic variations in several temperature-sensitive ion-channel mutations have been described in children with fever-triggered seizures. Classically, *SCN1A* mutations are known to cause temperature-sensitive epilepsy.[14] $GABA_A$-R γ-subunit mutations result in reduced expression and rapid endocytosis of $GABA_A$ receptors; these subcellular events are significantly enhanced at elevated temperatures.[3,15,16] Under experimental conditions, $GABA_A$ receptor-mediated gamma oscillations have been found to underlie the temperature-induced population spikes.[17] Decreased pre-synaptic release and post-synaptic GABA-R function have been documented in CA1 hippocampal neurons.[18,19] Interplay of genetic, inflammatory, and direct hyperthermia-associated factors contributed to the generation of prolonged febrile seizures in animal models.[9]

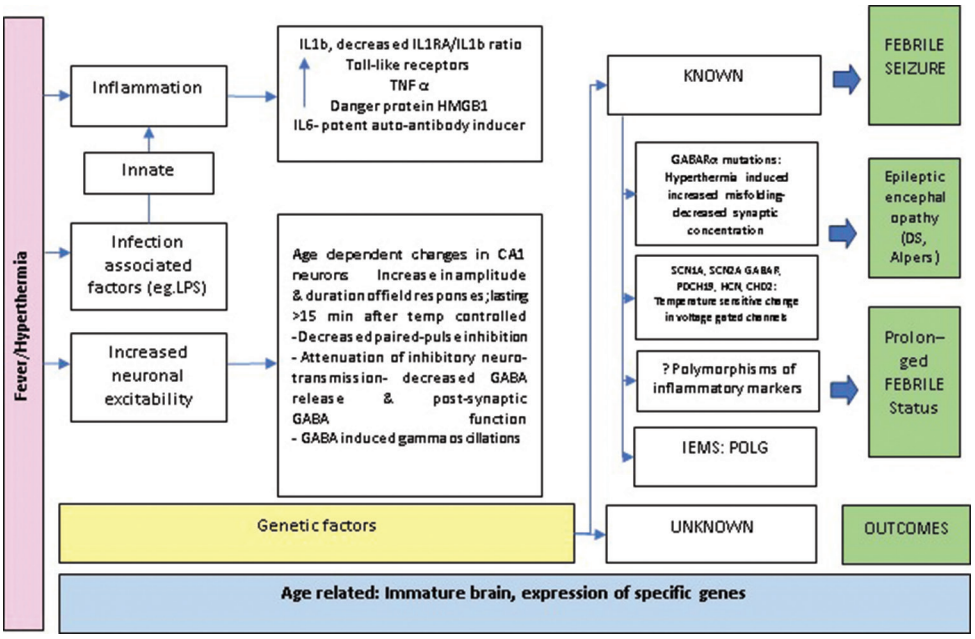

Figure 2: Possible pathophysiological mechanisms underlying fever-associated increased seizure sensitivity

Table 1: Summary of fever-triggered epilepsy syndromes

	CFS	FSE	FIRES	IHHE	AESD	ANE	RESLES
Age	6 months–5 years	6 months–5 years	2–17 yr (median: 8 years)	<2 years	10 months–4 years	9 months–6 years	~9 years
Phenotype	**Epilepsy predominant**				**Encephalopathy predominant**		
	CLINICAL SYNDROME				**CLINICO-RADIOLOGICAL SYNDROME**		
				Clinical features			
Time lag: fever & neurological symptoms	Minutes–hours	Minutes–hours	<24 h–14 days	Minutes–hours	1–2 days	1–3 days	1–2 days
Triggering factors	-	-	-	-	Infections: MC HHV6, influenza	Infections: MC HHV6, influenza	Infections: MC HHV6, influenza
Unique features	-	-	Explosive onset of RSE/ SRSE	Hemiconvulsive SE f/b hemiplegia lasting >24 h	FSE f/b seizure-free interval f/b secondary seizures b/w day 3-9	Acute onset encephalopathy, seizures after a prodromal illness	Acute onset encephalopathy, seizures after a prodromal illness
Course	Controlled without AEDs	Controlled with AED	RSE/SRSE, poorly responsive	Initial control f/b focal seizures on 75%	Controlled/RSE	Acute systemic inflammatory response	Improvement over 1 month irrespective of treatment
Outcome	Normal	Normal/increased susceptibility to secondary seizure	Chronic epilepsy, polymorphic	Focal, often refractory epilepsy; hemiparesis	Moderate-severe ID, epilepsy, focal neurological deficits	10%: normal 30%: mortality Epilepsy, motor deficits, ID	Normal
				Investigations			
CSF	Not indicated	Normal	Normal/pleocytosis with normal protein, OCB absent		Normal	Pleocytosis with normal/ elevated protein	Normal
Liver enzymes	Not indicated	Not indicated	Normal	Normal	Elevation ±	Elevated	Normal
Serum sodium	Not indicated	Not indicated	Normal	Normal	Normal	Not specific	Low
Autoimmunity	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Neuroimaging characteristics	Not indicated	Occasional structural malformations, doubtful causal association	Normal/nonspecific (B/L temporal, symmetric gray matter hyperintensities)	Acute: Hemispheric cytotoxic edema chronic: Hemispheric atrophy	Day 3-9: Subcortical WM diffusion restriction	Bilaterally symmetrical lesions in the thalamus (target sign), cerebral WM, cerebellum, brainstem	Reversible lesion with diffusion restriction in splenium/corpus callosum
Genetics	*SCN* family, *GABAR* family, *HCN* family	*SCN1A, GABARα, STXBP1, CDH2*	*SCN* family, *POLG*, *PCDH19*, ?IL-1β polymorphisms, ?unknown	-	Unknown	*RANBP2, CPT2*	Unknown
Differential diagnosis	Structural epilepsy	Structural epilepsy, Dravet syndrome, Dravet-like syndromes	Infectious encephalitis Autoimmune encephalitis/ epilepsy Dravet syndrome *PCDH19*-epilepsy PRES *POLG* (Alpers), citrullinemia, BTBGD	CFS, stroke	FIRES Autoimmune encephalitis/epilepsy Metabolic disorders	Leigh's disease Deep venous thrombosis	Infectious encephalopathy/ encephalitis

AESD: acute encephalopathy with biphasic seizures and delayed reduced diffusion, ANE: acute necrotizing encephalopathy of childhood, BTBGD: biotin-thiamine responsive basal ganglia disease, CFS: complex febrile seizure, FIRES: fever infection-related epilepsy syndrome, FSE: febrile status epilepticus, ID: intellectual disability, IHHE: infantile hemiconvulsion hemiplegia epilepsy syndrome, MC: most common, PRES: posterior reversible encephalopathy syndrome, OCB: oligoclonal bands, RESLES: reversible splenial lesion syndrome, RSE: refractory status epilepticus SE: status epilepticus, SRSE: super refractory status epilepticus, WM: white matter

Prolonged seizures appear to independently induce a cyclical cascade of inflammation and seizures. Seizures/status epilepticus results in activation on astroglia and microglia, release of cytokines (IL-1β, TNF-α, HMGB1), and activation of various downstream pathways such as NFkB induction, nuclear induction of cytokine proteins, and calcium-influx mediated activation of the kinase pathways. This further begets more seizure activity and increased permeability of the blood–brain barrier, leading to the recruitment of systemic inflammatory cells into the brain.[20]

In addition to the inflammatory cascade, long-term neurophysiological and possibly neuroanatomical changes occur in neuronal circuitry. Experimentally, increased inhibitory post-synaptic potentials (IPSP) have been observed 1 week after febrile status in rat pups, with paradoxically increased excitability.[21] This is due to activation of the "molecular inhibition excitation converter," the HCN (I_h) channels that are activated by hyperpolarization and result in a persistent hyper-excitable state in the hippocampus.[22,23] Another mechanism is the persistent potentiation of "depolarization-induced suppression of inhibition" (DSI). DSI is mediated by pre-synaptic cannabinoid type 1 (CBD1) receptor, activated by depolarization-induced retrograde endocannabinoid release in CA1 neurons. CBD1 receptors have been found to be upregulated following prolonged febrile seizures, hence the persistent potentiation.[24]

Although no gross neuronal loss has been observed in animal studies, increased sprouting of mossy fibers in granule cell and molecular layers and decreased number of cells that differentiate to excitatory amino acid transporter-3 (EAAT-3; function- synaptic reuptake of glutamate) containing cells have been observed after exposure to prolonged febrile status early in life.[25,26] The underlying pathogenesis of FIRES, and possibly IHHC, follows a similar pattern. The acute, explosive epilepsy in FIRES occurs following a time lag of a few days after an inciting febrile illness. It has been postulated that during this lag period, an imbalance between pro- and anti-inflammatory mechanisms occurs, tipping the scales toward seizures. Autoimmune and metabolic etiologies have been found in a small subset of cases; however, in the majority, extensive autoimmune and infective and genetic workup fails to disclose any causative associations. Moreover, the lack of a defined time interval between the onset of acute status epilepticus and evolution to chronic epilepsy has been cited as an argument against the pure acquired nature of FIRES; however, unknown or unidentified genetic factors may have a role to play.[27] Genetic mutations in sodium channels (*SCN1A, SCN2A*) and recently, Dynamin (DNM) *DNM1* gene, which codes for a membrane remodeling GTPase involved in membrane fission and is specifically expressed in the nervous system, have been implicated in a few cases.[28] *DNM1L* mutation has been described in association with a mitochondrial epilepsy syndrome with fever sensitivity and refractory status epilepticus in developmentally normal children and children with minor developmental delay.[29,30]

A recent study identified significantly higher Th1-associated cytokines (TNF-α, CXCL9, CXCL10, CXCL11), IL6, CCL2, CCL19, CXCL1, and chemokines in FIRES/FIRES-related disorders and FSE (CXCL9, CXCL10, CXCL19, and CCL19) when compared to chronic epilepsy [Figure 3].[31]

The Febrile Seizures Spectrum

Complex febrile seizures (CFSs)

CFSs are defined as seizures occurring in children aged 6–60 months with fever ≥38°C, lasting ≥15 min, more than one episode in 24 h or a febrile event having focal features in the ictal/post-ictal semiology,[32,33] CFS constitute approximately 20%–30% of all febrile seizures.[1,34] Recurrent or prolonged focal seizures evolving to generalized seizures lasting >30 min without regaining consciousness are termed as febrile status epilepticus (FSE). Infants <18 months at the time of 1st febrile seizure are at risk of CFS, whereas a lower degree of rise of body temperature and longer duration of recognized fever before FS and structural temporal lobe abnormalities (hippocampal malrotation or HIMAL) are associated with a greater risk of FSE.[35] In the FEBSTAT study, the risk of second FS of any type after a first FSE/SFS was not significantly different; however, the presence of baseline MRI abnormality and occurrence of FSE as the first FS was related to increased risk of recurrent FSE compared to the first episode of SFS.[36] The risk of developing epilepsy following febrile seizures has been reported to be 2%–7%;[1,34] however, the data for independent risk associated with SFS and CFS remains unclear. Complex FS and FSE have been previously postulated to increase the risk of hippocampal sclerosis and subsequent mesial temporal lobe epilepsy. In children with FSE, impaired hippocampal growth at 1-year follow-up was seen, both in children with acute hippocampal injury (T2 hyperintense hippocampi, with evolution to hippocampal sclerosis at 1 year) and those with normal imaging in the acute period.[37] Further long-term follow-up studies on long-term effects on hippocampal development are awaited.

Febrile seizure plus

Children with febrile seizure plus (FS+) experience febrile seizures beyond 6 years of age and/or associated afebrile seizures.[2] Cases with a family history of FS/FS + are designated GEFS-plus. Intra-familial phenotypic expression is heterogenous; 1/3rd experience only febrile seizures that may persist being 6 years age, 1/3rd have remote generalized afebrile seizures during childhood with remission in adolescence, and the remaining 1/3rd present with a variety of generalized epilepsies.[38]

Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy, SMEI) is characterized by fever-triggered, focal, hemiclonic/myoclonic seizures in infants below 6 months of age, evolving to a refractory epilepsy with polymorphic seizure semiologies and development arrest, with underlying SCN1A mutations that are believed to be causal.

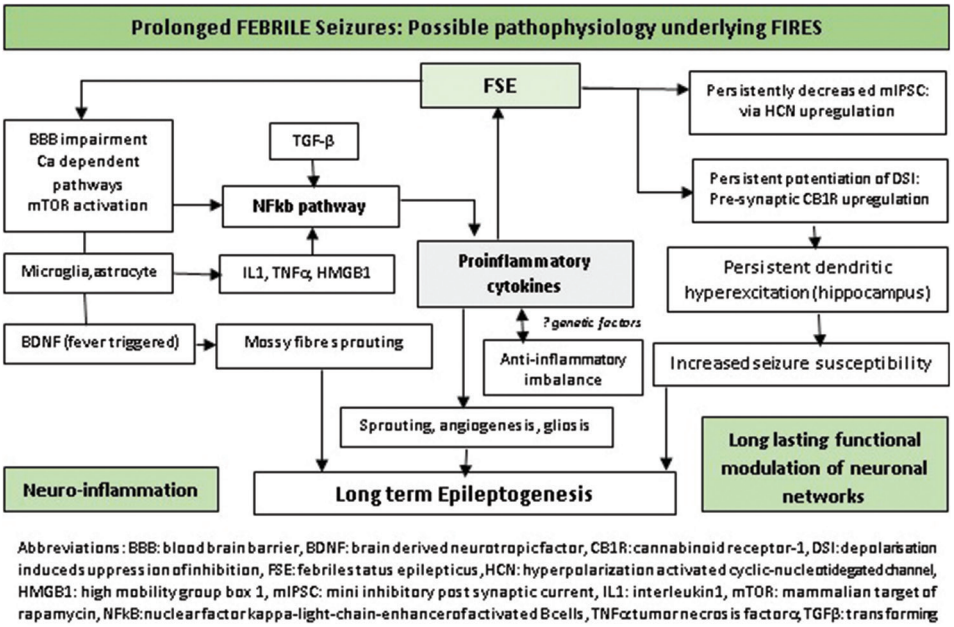

Figure 3: Postulated status epilepticus related inflammatory mechanisms and long-term effects underlying generation of ongoing acute and chronic seizures

Genetics

Linkage analyses have identified six loci for febrile seizures: *FEB1* (Chr8q18–q21), *FEB2* (Chr19p13.3), *FEB3* (Chr2q23–q24; 3A-*SCN1A*, 3B-*SCN9A*), *FEB4* (Chr5q14–q15; GPR98), *FEB5* (Chr6q22–q24), *FEB6* (Chr18p11.2), *FEB7* (Chr21q22), *FEB8* (Chr5q31; GABARG2), *FEB9* (Chr3p24.2-p23), *FEB10* (Chr3q26), and *FEB11* (Chr8q13; CPA6).[39,40] *SCN1A*, *SCN1B*, *SCN2A* (neuronal voltage gated sodium channels), and *GABARA1* (α1 subunit of $GABA_A$ receptor) are the common mutations underlying GEFS+.[41] De-novo SCN1A mutations underlie approximately 85% cases of SMEI; other putative genes include *SCN2A*, *SCN1B*, *SCN8A*, *GABARA1*, *GABARG2*, and *GABARB3*.[42] Recently, fever-sensitive seizures have been described with *STXBP1*,[43] *PCDH19*,[44,45] *SCN9A*,[46] *FGF13*,[47] and *HCN2*.[3]

NORSE and FIRES

1. **2a New-onset refractory status epilepticus (NORSE)** is a clinical presentation in a patient without active epilepsy or preexisting neurological disorder, with new-onset refractory status epilepticus, without clear acute or active structural, toxic or metabolic cause.[48]

1. **2b Fever-infection-related refractory epilepsy syndrome (FIRES)** is a subacute category of NORSE that requires fever 24 h to 2 weeks prior to the onset of status epilepticus, with or without fever at the onset of status epilepticus [Table 1].[48] The presence of fulminant onset of bilateral focal/generalized seizures or SE, poorly responsive to treatment for days or weeks, preceded by fever/infection occurring in school-aged children in the absence of previous neurological illness, infectious or metabolic etiology, abnormal behavior or movement disorder, positive neuronal antibody testing and progression to a state of chronic epilepsy immediately following the acute phase, frequently with moderate-severe neuropsychological impairment, are required for the diagnosis of FIRES. Elevated CSF protein or the presence of oligoclonal bands and response to immunotherapy can be present occasionally. Isolation of infectious agents from body or CSF in the absence of laboratory or imaging markers of encephalitis, presence of CSF pleocytosis without isolation of infectious agent (maybe SE rated), presence of symmetrical gray matter hyperintensities on T2 weighted MRI (can be immune-mediated/SE-related), and elevated lactate peak on MRS do not rule out FIRES.[27]

Acute encephalitis with refractory, repetitive, partial seizures (AERRPS)[49] and devastating epileptic encephalopathy in school-aged children (DESC)[50] have the same course and outcomes as FIRES; these are probably the same entities with different nomenclature.

Neuroimaging

In the acute stage, MRI is normal in 60% of cases; abnormal features encountered most frequently are T2 weighted/FLAIR hyperintensity in temporal lobes (~25%), basal ganglia, insular region, and leptomeningeal enhancement.[51,52] Generalized cerebral atrophy, mesial temporal sclerosis, and WM signal abnormalities are the most common abnormalities in the chronic stage.[51] In addition, extensive WM signal abnormalities, probably secondary to focal demyelination, are associated with poor outcomes.[52]

EEG

Interictal findings include diffuse slowing, focal or bilateral temporal, frontal or frontotemporal discharges,[53,54] and recurrent background extreme-delta brushes.[55] The ictal pattern consists of focal fast activity of >10 Hz of moderate

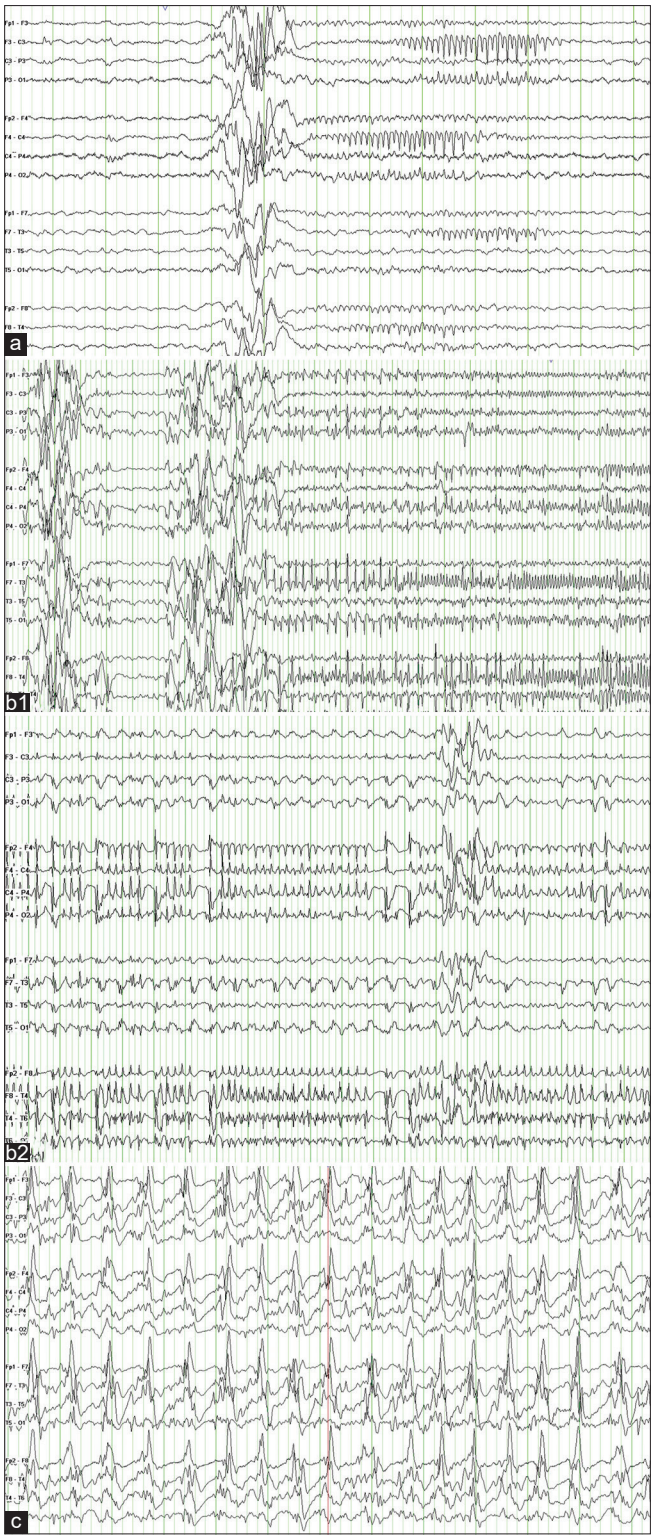

Figure 4: EEG patterns in FIRES. (a) Generalized burst of epileptiform discharges. (b) Two generalized bursts of discharges, followed by left temporal-occipital spike wave discharges evolving sequentially to low amplitude fast rhythm (1) followed by spike-slow wave discharges (2). Right sided leads show fast activity immediately post the generalized burst with evolves into slower spikes, and continues after the left sided ictal activity resolves. (c) Generalized slow spike wave discharges

amplitude with evolution to rhythmic spike and spike-wave complexes and with inter-hemispheric shifting of the ictal activity [Figure 4].[56]

Genetics

While no specific causative genetic mutations have been associated with FIRES to date, Alpers disease (*POLG* mutations), *PCDH19*, and *SCN1A*-related fever-triggered epilepsies remain close differentials. Recently, *DMN1L* gene mutations, coding for a dynamin-1-like protein that participates in the synaptic vesicle cycle of neurotransmitter release, have been reported with FIRES and fever-triggered epilepsy.[27]

Infantile hemiplegia hemiconvulsion with epilepsy syndrome (IHHE)

Infantile hemiplegia hemiconvulsion with epilepsy is a rare clinic-radiological syndrome, occurring in previously healthy children below 2 years of age. It presents acutely with febrile, focal, prolonged status epilepticus (lasting up to 24 h) with postictal hemiplegia and hemispheric cytotoxic edema on MRI [Table 1].[57] After a seizure-free interval of a few months to <3 years (mean: 1–2 years), spontaneous recurrent, often refractory, focal seizures ensue, with variable residual hemiparesis and hemiatrophy on neuroimaging.[58]

Infantile-onset hemiconvulsion hemiplegia epilepsy syndrome can be diagnosed in a child <2 years with new-onset refractory, unilateral, focal status epilepticus with ipsilateral hemiparesis lasting >24 h after SE, high-grade fever at the onset of SE, and unilateral abnormal imaging in the acute stage after exclusion of infectious encephalitides.[48]

Neuroimaging

Diffuse hemispheric cytotoxic edema with T2 and DWI hyperintense signal and corresponding hypointense signal on ADC maps, with subcortical predominance, is seen.[58-60] At times, mass effect over the opposite hemisphere is also observed. Over the next 8–15 days, edema decreases with pseudo-normalization of ADC values and persistent high T2 signal. Cerebral atrophy involving the pathogenic hemisphere sets in by 1 month [Figure 5].[58]

EEG

In the acute phase, the ictal EEG consists of bilateral or unilateral rhythmic (2–3 Hz), slow waves with intermixed spikes, sharps, and intermittent fast activity with an asymmetric expression over the affected hemisphere (with higher amplitude delta, and not infrequently, attenuation on the affected side). Frequent evolution of ictal rhythms can be observed. Post-ictally, high-amplitude slow waves can be seen over the affected hemisphere. In the chronic stage, focal EEG discharges may be observed.[57,58,61]

Etiology/Genetics

Classically, HHE is considered to be idiopathic; the term "symptomatic IHHE" has been used in the literature when the clinical mimicker is seen as a complication during the

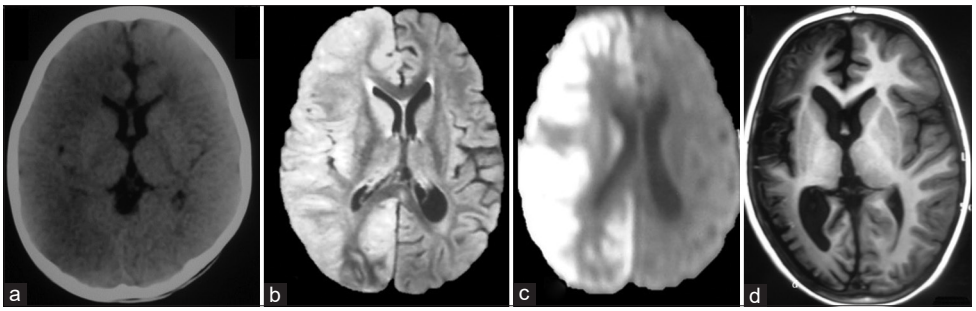

Figure 5: Infantile hemiplegia hemiconvulsion epilepsy syndrome (IHHE) (a) Noncontrast CT showing diffuse edema with loss of cortico-medullary junction differentiation of the right hemisphere, (b) FLAIR image showing right hemispheric cortical edema and caudate hyper-intensity with minimal midline shift anteriorly, (c) Right-hemispheric cortical diffusion restriction suggestive of cytotoxic edema, and (d) right-hemispheric cortical atrophy at follow-up

course of a preexisting disorder, such as Sturge–Weber syndrome, structural abnormalities such as agenesis of the corpus callosum, polymicrogyria–pachygyria–lissencephaly spectrum, associated with precipitating factors such as viral infections (HHV-6, HHV-7),[60] coagulation disorders without thrombosis (protein S deficiency, factor V mutation, *MTHFR* mutation) and *SCN1A* mutations.[58] The role of *CACNA1A* mutations has been postulated considering observation of hemispheric cytotoxic edema in patients with hemiplegic migraine and fatal, malignant hemispheric edema following trivial trauma in children. The role of genetic polymorphisms in inflammatory mediator genes is hypothesized.[58] Alternating hemiplegia of childhood (AHC) must be considered in cases with recurrent hemiparesis, with normal inter-ictal neurological examination initially, which is followed by a gradual decline over multiple attacks; AHC is associated with seizures in almost 50% of cases. Neuroimaging is normal at the onset but in older patients, cerebral and cerebellar atrophy may set in.[62]

Acute encephalopathy with biphasic seizures and delayed reduced diffusion (AESD)

This condition was initially described in Japanese/East Asian children. AESD is a severe fever-triggered epilepsy syndrome in children aged 10 months–4 years[63-67] with a distinct clinico-radiological profile. At the onset, prolonged febrile status (>30 min) and altered sensorium are noted. This is followed by a seizure-free period during which sensorium improves transiently, commonly to a persistent subnormal level and occasionally to the normal level with a normal neurological examination. Secondary seizures begin between days 3 and 9, commonly as clustered focal seizures with/without generalization, with associated worsening of sensorium. Long-term outcomes include moderate to severe intellectual disability, focal neurological deficits, and epilepsy. A milder phenotype with short initial febrile seizure followed by biphasic seizures at days 4–6, normal sensorium in between biphasic seizures, and normal neurological outcome. Associated characteristic neuroimaging is well described.[63]

Acute encephalopathy with febrile status epilepticus, acute encephalopathy with biphasic clinical course, and acute infantile encephalopathy predominantly affecting frontal lobes (AIEF) are terminologies that have been reported in the literature, which probably fall along the spectrum of AESD, with similar imaging findings, limited to frontal lobes in AIEF, with some variation in the clinical course and outcomes.

Neuroimaging

The pattern and evolution of neuroimaging findings are the hallmarks of AESD. Initial MRI on day 2 is normal. Subsequently, with the appearance of secondary seizures, MRI on days 3–9 shows bilaterally symmetrical, frontal or frontoparietal (with peri-rolandic sparing) subcortical white matter hyperintensity, most evident on DWI images with corresponding decreased ADC values [Figure 6]. Central sparing is associated with relatively milder presentations.[68] On T2 and FLAIR, linear U-fiber hyperintensity, more prominent than cortical hyperintense signal, is observed. After day 9, the subcortical DWI hyperintense signal normalizes with a corresponding increase in ADC values; cortical DWI hyperintensity becomes the most prominent feature between days 9 and 25. Imaging done beyond 2 weeks shows T2/FLAIR hyperintensity of subcortical white matter and cerebral atrophy.[63]

EEG

EEG features are often nonspecific, and features of nonconvulsive status epilepticus, electrographic seizures, lateralized periodic discharges, and lateralized slow waves have all been reported.[65]

Etiology

In contrast to the above entities, AESD is more commonly associated with infectious prodromes, of which influenza A and B and HHV-6 and 7 are the most common; others are varicella, mumps, respiratory syncytial virus, rotavirus, and streptococcus and H influenza.

Prognostic factors

Attempts have been made to elucidate markers that predict progression to biphasic seizures after febrile status and prognosis after AESD. Poor outcomes have been associated with the presence of involuntary movements and persistent coma prior to the onset of secondary seizures, extensive lesions with low ADC values involving anterior, posterior

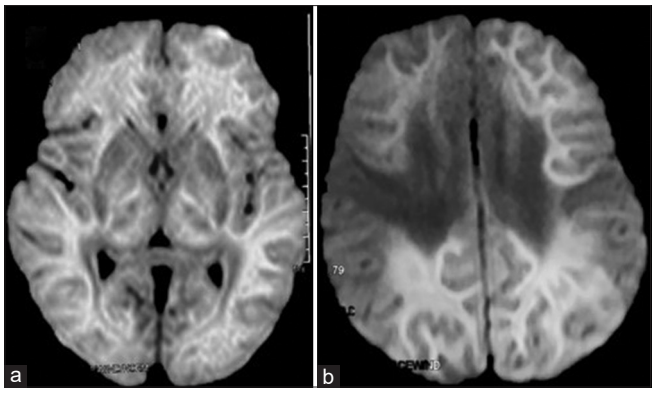

Figure 6: Acute encephalopathy with delayed diffusion restriction (AESD): DWI images showing diffuse white matter diffusion restriction affecting both hemispheres and posterior limb of the internal capsule (a) and central white matter and peri-rolandic sparing in "central sparing pattern" of AESD (b)

cerebrum, and basal ganglia, elevated alanine transferase levels,[64] aspartate aminotransferase (AST) within 24 h, elevated creatinine levels within 2 h, and presence of electrographic seizures.[65] Additionally, longer time to arousal or return to consciousness after FSE, elevated AST, ALT, lactate dehydrogenase, hyperglycemia, and hyperammonemia have been found to be related to a higher risk of developing secondary seizures after FSE; a scoring system for the same has also been developed.[69]

Acute necrotizing encephalopathy of childhood (ANE)

ANE is primarily a childhood disorder but has also been described in adults. Similar to AESD, viral prodrome is almost always preceded and is present at the time of onset of neurological symptoms. Classically, three stages have been described: prodromal, acute encephalopathy, and recovery. The prodrome usually manifests as a viral upper respiratory tract or gastrointestinal infection. This is followed by the onset of encephalopathy (~100%), seizures (50%–100%),[70-72] and focal deficits [Table 3]. Features of disseminated intravascular coagulation, shock, and multiple organ injury, and laboratory abnormalities such as elevated liver enzymes, hypoglycemia, and lactic acidosis can be present in variable combinations, suggestive of a systemic inflammatory response. The recovery phase is characterized by neurologic sequelae; normal outcomes are present in <10% and the mortality rate is estimated to be high at ~30%.[73]

Diagnostic criteria have been described for the diagnosis of ANE.[73] Sporadic ANE is diagnosed in the presence of acute encephalopathy following a febrile illness, presence of typical neuroimaging features, elevated CSF protein in the absence of pleocytosis, elevated aminotransferase with normal ammonia levels, and exclusion of clinical and radiological differentials.[73,94,95] In addition to sporadic ANE, if the patient has a family history of neurological illness (may be para-infectious), recurrent fever-triggered encephalopathy episodes, or additional MRI changes in any one area (medial temporal lobe, amygdala, claustrum, hippocampi, mammillary bodies, and spinal cord), familial/genetic ANE (ANE1) should be considered.[73,96,97]

Neuroimaging

While the clinical features of ANE are nonspecific, the neuroimaging findings are almost diagnostic. The "tricolor pattern," "concentric/laminar structure," or the "target-like appearance" of the thalamus is the most striking and consistent feature, most readily apparent on ADC images- innermost necrosis and hemorrhage, middle layer of cytotoxic edema, and outermost layer of vasogenic edema [Figure 7]. The brainstem, cerebellum, and cerebral white matter are commonly involved; spinal cord involvement can be seen occasionally. Involvement is usually bilateral; unilateral lesions are not uncommon.[73,98] Familial ANE has a predilection for the thalamus and pons rather than a more diffuse involvement.[72]

Etiology/triggering factors

Influenza A/B, H1N1, metapneumovirus, HHV6, HHV7, parainfluenza, varicella, enterovirus, rotavirus, rubella, coxsackievirus, measles, parvo B,[99] dengue,[100] E. coli,[98] and most recently, SARS-CoV[101] have been isolated; of these, influenza and HHV6 are the most common.[71,73,102]

Genetics

As ANE is rare, the true prevalence of familial/genetic ANE, known as ANE1, is not known. Approximately 31% of ANE1 have dominantly inherited *RANBP2* (Chr2) mutation,[103] with ~40%–50% penetration.[104,105] Carnitine palmitoyl transferase-2 (CPT2) gene is another gene implicated in ANE.[106] Digenic inheritance of both genes with fatal outcomes in a single family has also been reported.[107]

Reversible splenial lesion syndrome (RESLES)

In the spectrum of prodromal febrile encephalopathy/seizure clinico-radiological syndromes, RESLES falls toward the milder end. Clinically, it is characterized by a prodromal viral illness followed by the onset of neurological symptoms 1–2 days[63,108] (up to 10 days)[109] after fever onset. Encephalopathy lasting >12 h (54%), seizures (33%), sleepwalking, and delirious behavior are frequent neurological features.[63] Pleocytosis with normal/mildly elevated protein or normal CSF study and hyponatremia are the most common laboratory abnormalities.[63,108-110] Irrespective of treatment, normal outcome has been reported in all cases.

This entity was previously known as mild encephalopathy/encephalitis with a reversible splenial lesion (MERS) and has been revised recently revised to RESLES to incorporate all entities with transient reversible lesion with diffusion restriction. Another term, reversible splenium lesion with febrile illness (RESLEF), has been proposed to additionally include entities without encephalopathy but similar neuroimaging findings.

Neuroimaging

The MRI shows diffusion restriction limited to the splenium (MERS1), involving the entire corpus callosum

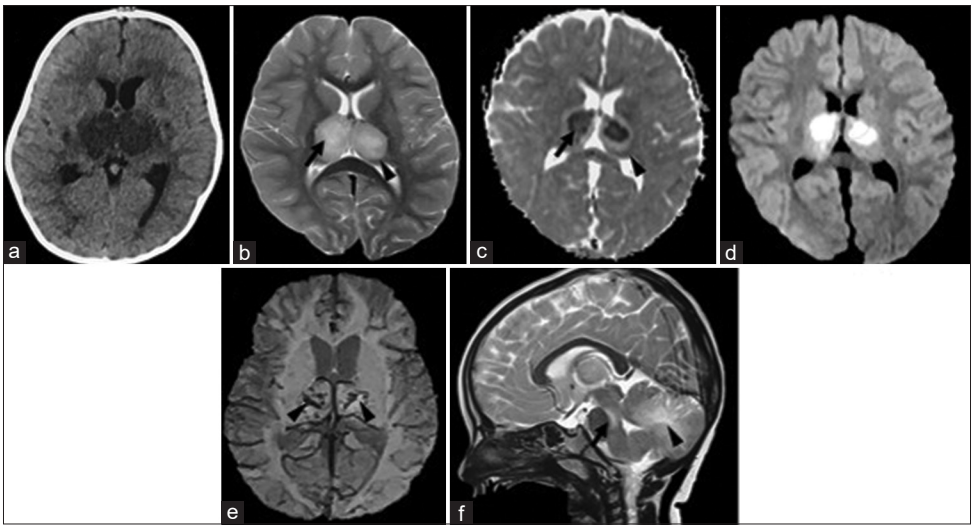

Figure 7: Acute Necrotizing Encephalopathy of childhood (ANEC): (a) Non-contrast CT showing bilaterally symmetrical thalamic hypodensity; (b) Bilateral symmetrical thalamic involvement with edema, T2 hyperintensity (arrowhead), central heterogeneous areas (arrow); (c) Central heterogeneous areas show cytotoxic edema with diffusion restriction and surrounding area of facilitated diffusion on ADC images, note the innermost area with hyperintensity consistent with necrosis giving classical Target-like appearance of thalamus; (d) DWI sequences with central areas of diffusion restriction; (e) foci of haemorrhage on SWI images (arrowheads); (f) Sagittal T2 images shows hyper-intensity in dorsal pons & cerebellar white matter

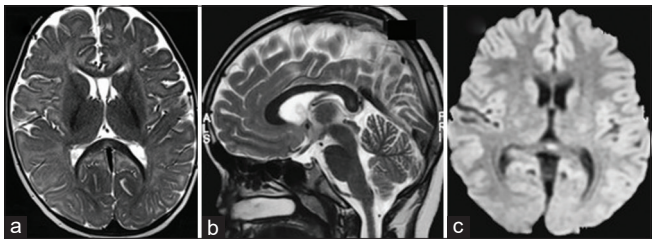

Figure 8: Reversible splenial lesion syndrome (RESLES): Axial (a) and sagittal (b) T2 images show focal, well-defined hyper-intensity in splenium; the same area shows diffusion restriction on DWI image (c). Abbreviations: AED: antiepileptics, AESD: acute encephalopathy with biphasic seizures and delayed reduced diffusion, ANE: acute necrotizing encephalopathy of childhood, DBS: deep brain stimulation, ECT: electroconvulsive therapy, FIRES: fever infection-related epilepsy syndrome, IHHE: infantile hemiconvulsion hemiplegia epilepsy syndrome, IvIG: intravenous immunoglobulin, KD: ketogenic diet

with/without extension to contiguous deep white matter (MERS2) [Figure 8]. Extra-splenial lesions involving subcortical white matter have been reported.[108] The lesions disappear on repeat imaging done 2–5 weeks after symptom onset.[108-110]

Investigations

An individually tailored approach consisting of detailed clinical evaluation and investigations as per the likely clinical possibilities is recommended [Table 2]. For any child presenting with fever and seizure that is not a febrile seizure, ruling out meningitis is a must. CSF microscopy, protein, sugars, and cultures along with blood and if required, urine cultures testing for common pathogens are the first-line investigations. Considering the clinical features and epidemiologically prevalent infections, testing for dengue, chikungunya, enterovirus, H1N1, varicella, scrub typhus, tuberculosis, E. coli, malaria, mycoplasma, and chlamydia needs to be considered. In immunocompromised patients, additional investigations may be required to rule out opportunistic infections as well.

Neuroimaging is indicated for all patients. Plain and contrast CT can help to diagnose acute hydrocephalus, basal exudates, bleeding, major sinus thrombosis, and infarcts. In cases where the workup for an infectious etiology is normal, MRI findings can play a discriminatory role and are helpful in deciding the next steps. The imaging findings may be normal or disclose nonspecific, or specific radiological findings such as ANE, AESD, or RESLES. Metabolic testing, including serum ammonia, lactate, TMS, and GCMS, may be included on a selective basis. A toxicology screen may be indicated if history is suggestive, and if negative, autoimmune testing as detailed in Table 2 should be considered. Thus, every attempt to diagnose conditions where targeted therapeutic interventions are available must remain a priority. At times, it may be necessary to do invasive investigations such as brain biopsy/muscle biopsy to diagnose conditions such as CNS vasculitis. Genetic testing (whole-exome sequencing with rapid turnaround time) should be sent if workup has been unrevealing, especially in all cases with ANE phenotype. With the upcoming role of inflammation and targeted therapies, there may be a potential role of serum and CSF cytokine profiles to tailor therapies in the future.

Management

There is a lack of robust evidence-backed protocols as these entities are rare. Of these, management of FIRES is the most challenging as by definition, it is refractory SE; in other entities,

the acute status decreases over time in the natural course of the disease. Management is based on two lines, namely status control and immunomodulation, as inflammatory/cytokine-mediated mechanisms are thought to play a major role in pathogenesis [Table 3, Figure 9].

Refractory/Super-refractory status epilepticus

Management protocols are available for the treatment of status epilepticus; it is often individualized for refractory and super-refractory status (RSE/SRSE). Following the failure of first-line anti-epileptic drugs (AEDs), pharmacological or therapeutic coma is used as second-line therapy. Drugs used include midazolam, pentobarbital, phenobarbitone, and inhaled anesthetics (thiopentone, propofol, and desflurane). Targeting burst suppression rather than electrographic seizure control was found to be associated with a trend toward better seizure control and GCS at 6 months follow-up; however, higher drug doses and a higher rate of hemodynamic

Table 2: Investigations and workup

First Line	
Serologic: Hemogram, bacterial & fungal cultures, VDRL, HIV1/2, Weil Felix, Flavivirus panel, Malaria antigen	
CSF: Routine examination, oligoclonal bands, bacterial & fungal cultures, PCR (HSV1/2, VZV, EBV), Genexpert	
Serum & CSF: IgG & IgM – mycoplasma, chlamydia, bartonella, Coxiella, shigella	
Nasal swab: H1N1, SARS-CoV	
Neuroimaging: Plain &Contrast enhanced MRI (T1, T2, FLAIR, DWI, ADC)[#]	
Metabolic profile: liver and renal parameters, serum electrolytes	
Epilepsy predominant phenotypes: EEG, continuous EEG monitoring for convulsive/nonconvulsive status	
Immunocompromised host (Additional testing)	
Toxoplasma, cryptococcus, tuberculosis, CNS fungi, virus (JCV, EBV, enterovirus, CMV, parvovirus, listeria, measles)	
Second-line investigations	
MRI: Normal/nonspecific/AESD/IHHE pattern	MRI: ANE/RESLES pattern
Metabolic: Serum ammonia, lactate, TMS/GCMS	Viral infectious workup
Autoimmune workup:	
NMD_A, VGK_C-LGI1, anti-GAD65, AMPA, GABAA, GABAB, Glycine receptor, CASPR2, DPPX, anti-Tr, amphiphysin, neuraxin-3α, CRMP5/CV2, anti-neuronal (Hu, Yo, Ri) antibodies	
Anti-TPO antibodies	
ANCA, ANA, anti-dsDNA, ESR, CRP, anti-Jo1, Ro, La, Scl-70, RF, TTG	
Third-line investigations	
Genetic testing: *SCN* family, POLG, *PCDH19, STXBP1, HCN2*, metabolic disorders	*RANBP2, CPT2*
Optional as required:	
PET (strong suspicion of focal structural epilepsy)	
CSF/serum cytokine profile (IL1, IL6)	
Muscle/Liver biopsy: Mitochondrial disorders	
Brain biopsy: exclusion of vasculitis/encephalitis	

[#]MR angiography/venography must be performed if suspicion of vascular event is high

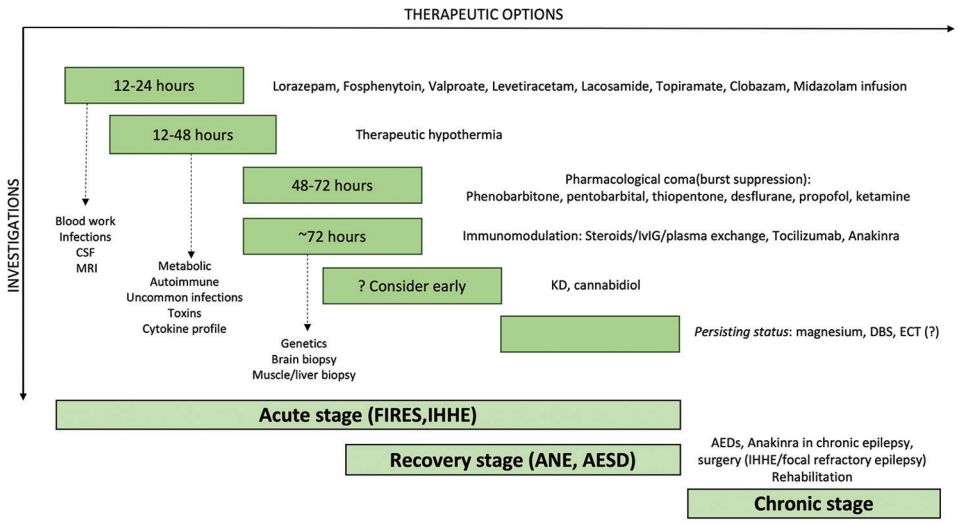

Figure 9: Summary of management in entities with refractory status

Table 3: Treatment options

Intervention	Dose	Comments
Super refractory status epilepticus		
Ketogenic diet	1:1-1:4	Effective in acute & chronic phase of FIRES[99] Anti-inflammatory effects[97] ?Better cognitive outcomes[101]
Cannabidiol	15-25mg/kg/day	Used as add on therapy in SRSE Found to be effective in decreasing seizure frequency & AED load in FIRES[102]
Therapeutic hypothermia	32-35^{0}C for 2-5 days, rewarming 1^{0}C/day to 36^{0}C	Better seizure control/outcomes when initiated early- within 12 hours to first 3-5 days after onset of neurological symptoms[103], shorter seizure duration & lesser chronic epilepsy in an SRSE (FIRES & non-FIRES) cohort[104]
VNS	-	Shown to have some efficacy in adult SE & NORSE, pediatric studies in RSE/SRSE lacking[105,106]
Magnesium sulfate	20mg/kg/hr, Max: 40mg/kg/hr	Successful in isolated FIRES cases Serum Mg level: 2-4mmol/L[107]
ECT	-	Effective in isolated case reports as last resort[108]
DBT	Centro-median thalamic nuclei stimulation	Case reports with limited effectiveness in preventing generalized seizures[109]
Immunomodulatory therapies		
Broad spectrum		
Pulse methyl prednisolone	20-30mg/kg/day x 3-5 days	Used as first line therapy for both epilepsy & ANE[70-72,110] No definitive data to support effect in FIRES Probably the only 1st line therapy effective in ANE (Dexamethasone used in some reports)
Intravenous immunoglobulin	2 gram/kg over 2-5 days	Probably not effective in FIRES spectrum, [27] unclear role in ANE
Plasma exchange	5-6 cycles over 5-10 days	Probably not effective in FIRES spectrum, [27] unclear role in ANE
Rituximab	375mg/m^2	Unclear efficacy[27]
Targeted therapies		
Tocilizumab	<30kg: 12mg/kg >30kg: 8mg/kg*	ANE: Excellent outcomes have been reported in 3 children[111] FIRES: Favourable responses observed in isolated case reports & series[112,113]; also in adults with NORSE[114] *doses used vary in case reports
Anakinra	1-10mg/kg/day, max 200mg/day[115]	IL-1R antagonist FIRES: Excellent[116] to moderate response[117]&, some response in addition to DBS[109] in acute stage, moderate response; excellent seizure control in chronic phase[118]

Abbreviations-DBS: deep brain stimulation, ECT: electroconvulsive therapy, VNS: vagal nerve stimulation

instabilities without longer PICU stay/hospitalization were also present.[111] Duration of inter-burst intervals was not found to be significant in predicting RSE control.[112] Midazolam was found to carry a better side effect profile and shorter intensive care unit care stay as compared to thiopentone in an adult study; similar comparisons in the pediatric cohort have not been attempted. These findings may be applicable to pediatric cases as well.[113] High-dose phenobarbitone infusion (1–3 mg/kg/h) has been shown to be effective in SRSE.[114] High rates of seizure recurrence after tapering pharmacological coma have been reported. Additional therapies include early initiation of ketogenic diet (KD), therapeutic hypothermia, cannabidiol, and magnesium sulfate, of which KD appears to be the most effective. In a recent metanalysis, KD was the only therapy related with positive outcomes when used in the acute stage.[115]

Immunomodulatory therapies

The use of corticosteroids, intravenous immunoglobulin, and plasma exchange[49] has not been associated with favorable outcomes. Of these, the use of high-dose pulsed intravenous corticosteroids as a first-line agent is almost universal. Intravenous immunoglobin alone or paired with pulsed steroids does not appear to provide additional benefit over pulsed steroids alone in FIRES.[116] However, all three probably do not have any significant effect on seizure control in FIRES and related epilepsy phenotypes. High-dose intravenous corticosteroids (methylprednisolone or dexamethasone) are probably the most effective in ANEC and probably the only treatment, if at all used, in RESLES. Of the other immunomodulatory therapies, anakinra and tocilizumab appear to be promising for FIRES and ANE, respectively [Table 3].

Ketogenic diet

The ketogenic diet (KD), a low-carbohydrate, high-fat diet, deserves a special mention among the myriad of available treatment options. This is the only modality to have shown statistically significant benefit in FIRES patients, especially when used in the acute phase.[115] It is postulated to have antiepileptic, immunomodulatory, and neuroprotective effects through multiple mechanisms of action.[75] Time to

cessation of SE after KD initiation varied from 1–10 days[117] to 4–6 days,[74] maximum up to 19 days[118] in three different studies. Oral and parenteral formulations are available in the market; indigenous ingredients can be used to tailor-make the diet where these are either not available or affordability is an issue. Planning should probably commence at the time of initiation of pharmacological coma, and early initiation should be considered for optimal outcomes once it is clear that early immunomodulatory therapies (steroids/immunoglobulins) are probably not working.

Conclusions

Fever-triggered epilepsy and encephalopathy syndromes present a wide spectrum of clinical and radiological phenotypes. The knowledge of underlying pathophysiological mechanisms is still evolving. An interplay of brain immaturity, genetic predisposition, and inflammation seems likely. Awareness of these entities is important for the prompt institution of immunosuppressive and immunomodulatory treatments. As these are individually rare entities, long-term, prospective, multicentric studies are required to improve the understanding on treatment strategies and long outcomes.

Search strategy and selection

References for this review were identified by searching PubMed for articles published in English between June 1, 1993 and May 31, 2020 and by further examining the reference lists from relevant articles. Combinations of the following terms were used: "febrile seizures," "febrile status epilepticus," "encephalopathy," "inflammation," "fever infection-related epilepsy syndrome of childhood," "new-onset refractory status epilepticus," "acute encephalopathy with delayed diffusion restriction," "infantile hemiconvulsion hemiplegia epilepsy syndrome," "reversible splenial lesion syndrome," and "genetics." The final reference list was generated based on the relevance to the scope of this review.

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Conflicts of interest

There are no conflicts of interest.

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