Febrile Infection–Related Epilepsy Syndrome: Clinical Review and Hypotheses of Epileptogenesis

Andreas van Baalen[1] Annamaria Vezzani[2] Martin Häusler[3] Gerhard Kluger[4,5]

[1] Department of Neuropediatrics, Christian-Albrechts-Universität zu Kiel, University Medical Center Schleswig-Holstein, Kiel, Germany
[2] Department of Neuroscience, IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri," Milano, Italy
[3] Division of Neuropediatrics and Social Pediatrics, Department of Pediatrics, University Hospital, RWTH Aachen, Aachen, Germany
[4] Neuropediatric Clinic and Clinic for Neurorehabilitation, Epilepsy Center for Children and Adolescents, Vogtareuth, Germany
[5] Paracelsus Medical University Salzburg, Austria

Address for correspondence Andreas van Baalen, MD, Department of Neuropediatrics, Christian-Albrechts-Universität zu Kiel, University Medical Center Schleswig-Holstein, Building 9, Arnold-Heller-Str. 3, 24105 Kiel, Germany (e-mail: van.baalen@pedneuro.uni-kiel.de).

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Abstract

Febrile infection–related epilepsy syndrome (FIRES, AERRPS, or DESC) is one of the most severe, mostly irreversible, and presumably immune-mediated epileptic encephalopathies affecting healthy children. Refractory status epilepticus or a cluster of seizures start a few days after the onset of an acute febrile illness; however, encephalitis cannot be proved. Sequelae of FIRES are drug-resistant epilepsy and neuropsychological impairments occurring without latency. Clinical knowledge is limited because FIRES is sporadic and extremely rare. Therefore, based on literature and our data, this review includes clinical features, terminology, epidemiology, diagnostic criteria and procedures, differential diagnoses, acute and chronic therapeutic options, and outcome data. Particular attention is paid to the epileptogenesis. We hypothesize that FIRES is an immune but not an autoimmune disease and discuss GABAergic therapy at high doses, avoidance of burst-suppression coma, and early introduction of enteral or even parenteral ketogenic diet as the most promising treatment. The lack of evidence requires both a network and a multinational web-based clinical registry to define the clinical spectrum for improving diagnosis and treatment and at the very least, to clarify the cause of FIRES. We conclude that the term "fulminant inflammatory response epilepsy syndrome" may be more appropriate.

Keywords
- encephalitis
- encephalopathy
- epilepsy
- FIRES
- immunity
- inflammation
- status epilepticus

Introduction

If a previously healthy child presents a very close temporal relationship to a short febrile illness, often after short recovery, with an explosive onset of a severe status epilepticus (SE) refractory to even anesthetics and if infectious encephalitis was excluded, then "febrile infection–related epilepsy syndrome" (FIRES) should be suspected,[1] now being an important differential diagnoses of refractory SE (see ►**Fig. 1**).[2] Considering the close temporal relationship to febrile illness, an autoimmune etiology has initially been considered as one important hypothesis. This, however, seems increasingly unlikely, as no antineuronal autoantibodies and no response to immunotherapy have been commonly reported.[3] In general, diagnostic studies remain negative or unrewarding, leaving the etiology of FIRES unclear. As a result, alternative hypotheses of epileptogenesis are presented.

Positive findings were more likely to be a result of the unusually high epileptic activity; hence, antiepileptic treatment is extremely difficult. Permanent epilepsy and

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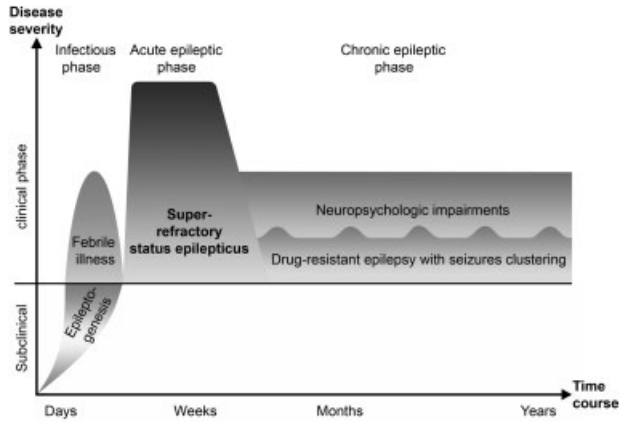

Fig. 1 Schematic illustration of the clinical course of FIRES.

handicaps are the consequences, although only few patients developed mild learning difficulties or no neurologic sequelae (►**Table 1**).[4]

Despite lack of biomarkers, early diagnosis is important to guide the treatment, for example, to select the optimal first-line therapy. This may optimize the outcome. As FIRES is extremely rare, this sudden and severe epileptic encephalopathy is challenging. Therefore, we hope that this clinical review may help to overcome FIRES.

Terminology

Patients fulfilling the clinical criteria of FIRES have been reported since 1961,[5] later using the terms "AERRPS" (acute encephalitis with refractory, repetitive partial seizures) as preferred in Japan[6] or "DESC" (devastating epileptic encephalopathy in school-aged children) as used in France.[7] Because of the lacking evidence on inflammation in cerebral spinal fluid (CSF), neuroimaging, and brain biopsies in our first three patients (brain biopsies performed in two patients revealed microglia activation, reactive astrogliosis, and no inflammatory changes in both),[8] we have concluded that the typical leucocyte tissue infiltrate associated with infectious encephalitis is not likely involved in this encephalopathy and that extensive neuronal excitation is a key feature of neuronal damage (see ►**Fig. 2**). Therefore, we first proposed the more descriptive term "fever initiated refractory (epileptic) encephalopathies (FIRE)." Olivier Dulac has then proposed to add an "S" because "FIRES" occurred mostly in school-aged children leading to the term "febrile infection responsive epileptic encephalopathies of school age,"[9] which we finally changed to "febrile infection–related epilepsy syndrome." The latter term more clearly highlights the concept of a characteristic set of clinical features with age-related onset also in preschool children. The cause is rather an immune reaction to an infection than fever.[1] "Fever-induced refractory epileptic

Table 1 Clinical features of FIRES

Age of onset: 2–17 (median 8) y[71]
Medical history: febrile seizures in rare cases, no epilepsy or other chronic disease, normal psychomotor development
Family history: uninformative, e.g., no allergies and especially no other family member with FIRES
Prodromal phase:
Different types of febrile infections often flu-like
Frequently followed by an afebrile and asymptomatic interval of 1–2 days result in a consistent neurologic syndrome
Neurologic syndrome:
Peracute/explosive onset of multifocal or generalized seizures of different types directly evolving into super-refractory status epilepticus
Without other neurological features (pure seizure-phenotype)
EEG: global slowing or multifocal discharges with bilateral frontotemporal predominance, or both
CSF: normal or pleocytosis, normal protein concentration, no oligoclonal bands
MRI (during the acute phase of status epilepticus):
None or nonextensive bitemporal or diffuse abnormalities
Sporadic involvement of the basal ganglia, diffuse cortical edema, and/or hydrocephalus
Cause: extensive infectiologic (e.g., brain biopsies),[58] metabolic (e.g., muscle biopsy), and genetic investigations (e.g., *POLG, SCN1A, PCDH19* genes, CNVs, exome sequencing)[16] without causative findings
Coexisting autoimmunities: some patients with autoantibodies (e.g., TPO or GluR antibodies)
Treatment:
Resistance to nearly all drugs and even anesthetics
Outcome:
Almost always chronic epilepsy without silent period
Often global brain atrophy after a few weeks with mild-to-severe neuropsychologic impairments

Abbreviation: FIRES, febrile infection-related epilepsy syndrome.

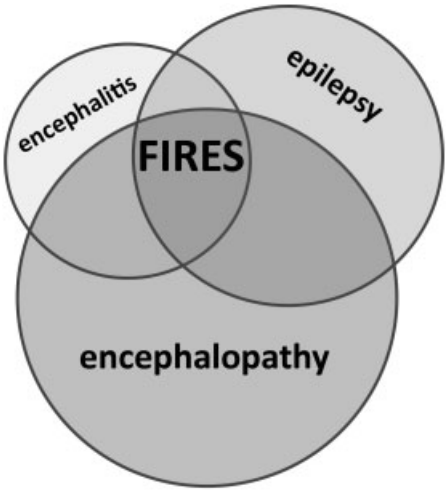

Fig. 2 Model of the phenotypic overlaps with FIRES.

encephalopathy in school-age children," however, is still the preferred term in France.[10] It is controversial whether FIRES is a syndrome or whether the causation is heterogeneous.[11]

In addition, there is an ongoing discussion, whether AERRPS, DESC, FIRES, NORSE ("new-onset refractory status epilepticus"), and "idiopathic hemiconvulsion-hemiplegia and epilepsy" in infants should be grouped under the concept of "acute encephalopathy with inflammation-mediated status epilepticus" (AEIMSE) based on their similar characteristics.[12–14] In contrast to FIRES, however, AERRPS is associated with higher and longer fever.[6] NORSE occurs in young adults, not always with a preceding febrile illness, has a clear female predominance, and responds to immunotherapy.[15]

Epidemiology

Approximately 100 cases have been published worldwide. With an estimated incidence of 1/1,000,000 and an estimated prevalence of 1/100,000 in Germany,[3] FIRES has a higher prevalence as the important differential diagnoses Alpers–Huttenlocher syndrome (0.7/100,000) and pyridoxine-dependent epilepsy (0.2/100,000) (Orphanet Report series—prevalence of rare diseases: bibliographic data—March 2016—number 2). Whereas there is a male predominance, neither an ethnic predisposition nor family cases have been published so far. This information can unburden worried parents, if a younger sister or brother reaches the same age of onset and develops a febrile illness. Due to lack of biological markers, the diagnosis is usually made on clinical grounds once differential diagnoses have been excluded (http://rarediseases.org/rare-diseases/febril-infection-related-epilepsy-syndrome-fires/). Therefore, FIRES may be underdiagnosed and, for example, misdiagnosed as presumed virus encephalitis due to features very closely resembled to those of FIRES, so the true incidence and prevalence may be higher.

Mechanistic Hypotheses of Epileptogenesis

In 1961, Lyon and colleagues first reported children with "an acute encephalopathies of obscure origin," finally suspecting an "acute toxic encephalopathy."[5] The clinical course and features very closely resemble those of FIRES. Half a century later, despite modern diagnostic methods, the origin has not yet been clarified. Furthermore, ketogenic diet (KD)[17–22] and phenobarbital[8,23] seem to be more effective than recent therapeutic options.

The proximity to a preceding febrile illness as a "condition sine qua non" makes it likely that FIRES is an immune disorder triggered by the infection. In contrast to febrile SE, SE in FIRES begins days after onset of fever. In addition, fever at onset of SE is often low grade or even absent, which argues against an acute fever-induced inflammatory process. Still, systemic and brain-born proinflammatory cytokines (perhaps the "toxic" agents supposed by Lyon and colleagues) during the preceding infection may elicit a process, which progressively lowers seizure threshold with delay.[24–26] Recent discussion has centered on the likelihood that the release of inflammatory molecules following systemic infection primes the activation of innate immunity mechanisms in glial cells, neurons and cellular components of the blood–brain barrier (BBB) in seizure-prone brain areas, giving rise to a neuroinflammatory cascade which in turn plays an important role in epileptogenesis.[12,27–30]

The potential role of neuroinflammation (cytokines and related effector molecules released by brain resident cells) in FIRES-associated epileptogenesis is based on experimental findings in animal models of infection[31,32] and of febrile and afebrile SE later developing epilepsy.[33,34] Neuroinflammation is a consequence of innate immunity activation, which occurs rapidly (within hours) and persists for several days after an epileptic insult (e.g., infection plus a second hit, febrile and afebrile SE), and in all these models epilepsy develops with a delay. This is compatible with FIRES where unremitting seizures begin days after febrile infection. This delay is not against the hypothesis that neuroinflammation plays a pathogenic role for the following reasons. First, we think that it is the concerted action of neuroinflammation triggered by the inciting event itself (e.g., the infection) and other subclinical pathologic changes (e.g., acquired or based on genetic predisposition, or both) that make the brain tissue capable of generating spontaneous seizures. These concomitant processes may take time to develop and interact in a synergistic and pathologic manner. In this context, neuroinflammation should be considered as a mechanism, which lowers seizure threshold rather than triggering seizures. Indeed, a transient exposure of infant rodents to agents mimicking bacterial (i.e., lipopolysaccharide) or viral (poly I:C) infections triggers a rapid and transient induction of specific inflammatory molecules in the brain (including the danger signal protein high mobility group box 1, interleukin [IL]-β, tumor necrosis factor-α, prostaglandin PGE2, and the complement system). This phenomenon is associated with a long-term reduction of seizure threshold lasting until adulthood and with an enhanced animal's propensity to develop comorbidities

(such as anxiety and cognitive deficits).[31,32] The mechanisms underlying these long-term modifications in brain physiology and excitability include post-translational changes in neuronal voltage-gated and receptor-coupled ion channels, alteration of glutamate and GABA release as well as their cellular reuptake, modifications in glutamate and GABA receptor trafficking at neuronal membranes, and deficient buffering capacity of astrocytes for rapid removal of extracellular K^+ and glutamate.[35] Moreover, up to 5% of the coding genes can be transcriptionally altered long term by a transient inflammatory challenge early in life. Essentially, at the time of insult, the brain tissue will react with a homeostatic attempt to reestablish normal tissue physiology. For example, in addition to proinflammatory mediators with a potential pathogenic role, there is a surge of anti-inflammatory molecules apt at controlling the inflammatory cascade and preventing tissue dysfunction. It is likely that the lack of efficient resolution in the neuroinflammatory process rather than the inflammatory surge will determine if this process becomes pathogenic. Accordingly, there is evidence that endogenous anti-inflammatory mediators, such as the IL-1 receptor antagonist[36] or the complement inhibitor CD59,[37] are inefficiently expressed during epileptogenesis and in human epileptogenic brain tissue.[38] The time for imbalance between pro- and anti-inflammatory molecules to take place can also explain the delay between the inciting event producing the surge of neuroinflammation and the onset of the disease (see ►**Fig. 3**).

Recent reports on intrathecal overproduction of proinflammatory cytokines and chemokines in AERRPS support this impact of neuroinflammation in epileptogenesis developing in these clinical conditions. Hereby, intrathecal inflammatory mediators, reflecting their production from brain cells, may be both cause and consequence of seizures as an exaggerated immune response in the brain may also occur secondary to refractory SE.[39,40] Indeed, experimental models of SE have shown that once seizure activity emerges and recurs, it can be itself a trigger of neuroinflammation and contributes to perpetuate innate immunity activation in seizure-exposed brain areas. This phenomenon may activate a vicious cycle that in turn fosters aberrant hyperexcitability; therefore, a prolonged condition of ongoing seizures can be generated.[12] Animal studies support whether an inflammatory response is sufficient to lower seizure threshold persistently for days to weeks.[31,32] Alternatively, but not mutually exclusive, a structural remodeling process of brain tissue or networks may permanently alter and increase excitability.[41] During postnatal development, cytokines are notably known to affect neuronal stem cells proliferation/migration, axonal guidance, synaptic connections and functions.[42]

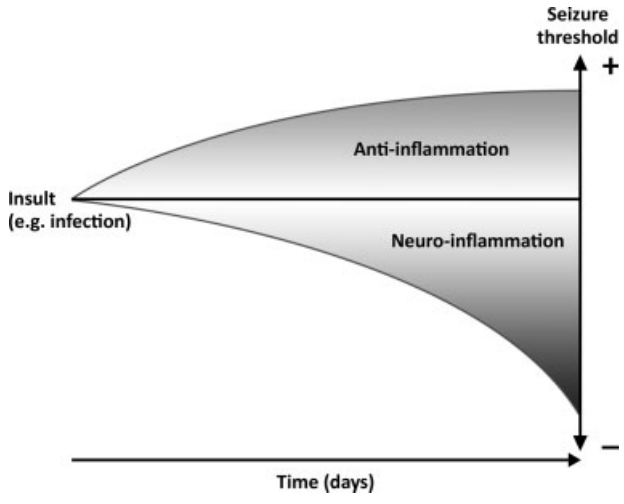

Fig. 3 Model of the seizure threshold in FIRES.

Although it is well known that the peripheral immune system is functionally and anatomically connected to the nervous system, the mechanisms underlying a central inflammatory response following peripheral inflammation are not precisely known as of yet. Proposed routes of peripheral-central two-way immune communication include the BBB allowing leukocytes and blood-born cytokines and related molecules to enter the brain under inflammatory condition,[43,44] the circumventricular organs that are devoid of a BBB, the hypothalamic-pituitary-adrenal (HPA) axis, and the vagal nerve reflex.[45,46]

Besides inflammation, several other potential causes such as encephalitis, autoimmune or metabolic diseases, and chronic epilepsy with explosive onset have been suspected and discussed in literature, but there are more arguments against than for these causes (►**Table 2**). The lack of an interval for epileptogenesis between the acute phase of SE and the immediately following chronic epilepsy is a strong argument against a purely acquired disorder but for an epileptogenic trait unmasked by a febrile infection.[47] So far, the causes and mechanisms of this extremely active epileptogenic process (both onset and maintenance) are still unknown. An immune-triggered metabolic disease or channelopathy may have relevance as well.[13,48,49]

In summary, the "toxic" agents, proposed by Lyon and colleagues to be causative, may be represented by ictogenic cytokines. FIRES is likely to represent an immune- (inflammatory-) but not autoimmune- (i.e., antibody-) mediated epileptic encephalopathy. The immune response to a febrile illness or infection affecting the brain elicits an explosive onset of intractable seizures; hence, the term "fulminant immune response epilepsy syndrome" seems to be more appropriate. The exact underlying pathogenic process, however, which leads to seizures when the febrile illness is often already finished, is unknown. The epileptogenesis needs a number of days to generate a massive excitability lasting days to weeks and thus raising the main question: which pathologic process or combination of brain alterations can initiate and maintain this extraordinary high and long-lasting epileptic activity resulting in global brain atrophy in many cases? For these reasons, in analogy, the term "epilepsia totalis continua" seems adequate as well.

Diagnosis

As there is currently no known cause of FIRES, no specific test is available to prove the diagnosis. The diagnosis depends on clinical grounds ruling out treatable and not treatable

Table 2 Discussion about the cause of FIRES

	Pros	Cons
Encephalitis	Febrile infection triggered	Different infections resulting in FIRES
		Biphasic course (infection → SE) in many cases
		CSF, MRI, and brain biopsies without typical findings of encephalitis
		Seizure control in the acute phase more difficult than in encephalitis
		Epilepsy without a latent period after SE
		Risk of postencephalitic epilepsy (0–33%)[99] less than in FIRES (nearly 100%)
Inflammation	Febrile infection triggered	No evidence of cerebral inflammation (e.g., CSF, MRI, and brain biopsy)
Autoimmune disease	Interval between first signs of infection and first seizures	Peracute, but not subacute onset of seizure activity in FIRES
		Seizures exclusively, i.e., no memory deficit, dyskinesia, and/or psychosis
		No oligoclonal bands and no pleocytosis in CSF
		No MRI and brain tissue findings suggestive of encephalitis
		To date, negative antibody findings in most cases
		No response to immunotherapy in most cases
Metabolic disease	Long duration of massive excitation	Late age of disease onset and no neurological deficits prior FIRES
	Major and progressive brain atrophy	No relapse
	Basal ganglia involvement	Basal ganglia involvement due to SE
	KD often effective	KD is nonspecific (with antiepileptic and anti-inflammatory effects)
Chronic epilepsy	Frontotemporal lobe predilection of discharges	For example, *POLG1* mutations cause a syndromic epilepsy with occipital predilection
	Epilepsy without a latent period after SE	Global brain atrophy likely not caused only by excitation

Abbreviations: KD, ketogenic diet; SE, status epilepticus.

infectious, alternative toxic, metabolic, and genetic causes in children who develop a super-refractory SE (i.e., SE that continues or recurs 24 hours or more after the onset of anesthesia)[11] in the temporal context of a febrile illness (►**Table 3**). Infectious disease should especially be considered in case of CSF pleocytosis, which is relatively uncommon (i.e., 4–8%) among children with prolonged seizures, even in the presence of peripheral leukocytosis.[50,51]

The increasing recognition that post- or parainfectious seizures and SE previously attributed to viral etiologies can be immune mediated or of genetic origin has led to a paradigm shift in the diagnostic approach. In autoimmune encephalitis, behavioral alteration, cognitive or memory impairment, and dyskinesia predominate but not seizures. FIRES, in contrast, is monosymptomatic with pure but massive seizure activity. The absence of CSF pleocytosis does not rule out an unrecognized autoimmune etiology. Seizures of autoimmune etiology are often resistant to conventional antiepileptic drugs but usually respond to immediate immunotherapy.[52] Therefore, early diagnosis is needed. After infectious encephalitis was excluded and while awaiting the results of the antineuronal autoantibodies, empiric immunotherapy should be commenced. If no antineuronal autoantibodies were identified, serum and especially CSF should be tested in research laboratories for the identification of new antibodies (►**Table 4**).[53–55] However, absence of detectable antineuronal autoantibodies and no response to immunotherapy do not exclude an autoimmune encephalitis.[56]

Differential Diagnoses

The complete clinical spectrum of FIRES is still unknown because of the lack of biological markers or genetic testing. Accordingly, a wide range of diseases with similar presentations is described and should be taken into account (►**Table 5**); hence, patients must undergo extensive investigations to exclude infectious, toxic, metabolic, or genetic causes that may be specifically treatable.[53,57] Still, extensive investigations for infectious agents (e.g., next-generation sequencing

Table 3 Inclusion and exclusion criteria of FIRES

Diagnostic criteria for FIRES:
SE or fulminant onset of bilateral focal or generalized seizures of different types for days or weeks despite treatment
Illness with fever or other clinical evidence suggestive of infection preceding seizures
Absence of previous neurological disease
Absence of evidence for infectious encephalitis and metabolic disorders
Absence of abnormal behavioral and movement disorders
Negative neuronal antibody test results
Drug-resistant focal epilepsy and neuropsychological impairments immediately following the phase of high seizure frequency in nearly all patients
Age of onset is childhood with peak onset in school age
Uncommon clinical and laboratory features in FIRES:
Elevated protein or presence of oligoclonal bands or both in CSF
Response to immunotherapy
Clinical and laboratory features not disclosing FIRES:
Detection of infectious pathogens in specimens not obtained from CSF
Detection of infectious pathogens in CSF without otherwise evidence of encephalitis in CSF or MRI
CSF pleocytosis without proven central nervous infection: may be induced by SE or immune-mediated[50]
Nearly symmetric gray matter hyperintensities on T2-weighted MRI (e.g., basal ganglia): may be induced by SE[59,100] or immune mediated[101]
Lactate on MRS
Muscle mtDNA depletion

Abbreviation: SE, status epilepticus.

microbiome approaches in brain biopsies)[58] and other etiologies are often negative. Transient as well as irreversible cerebral MRI abnormalities associated with SE can occur in cortex, hippocampus, white matter, thalamus, corpus callosum, cerebellum, and brain stem, but are rare. In consequence, differential diagnosis should always include epileptogenic causes.[59–62] Only in single cases, causative mutations[63,64] or sequence variants[3,16] of unclear clinical significance have been found. However, an increasing number of patients with noninfectious, mostly autoimmune, encephalitis have been identified in the past 10 years.[56] Immune-mediated encephalitis with antineuronal autoantibodies rivals viral etiologies as a cause of encephalitis.[65] This entity has become an important component of encephalitic differential diagnosis. The exact diagnosis is important, since some of these diseases are treatable (►**Table 5**).

Treatment Options

Acute Phase

Treatment is most frustrating and, likely, cannot be effective before the highest period of seizure activity has passed by itself. In addition, very high drug doses may be necessary for seizure reduction because of the extraordinary high epileptic activity. Thus, multiple different therapeutic options have been reported in small case series demonstrating that no one is superior, with the exception of KD. Systematic studies are lacking (►**Table 6**).

Because FIRES is an exclusion diagnosis and recently recognized autoimmune epilepsies with antineuronal autoantibodies as the most important differential diagnoses of immune-mediated seizures since they are potentially immune sensible, first-line immunotherapy should be given, despite nonresponse usually in FIRES. Plasma exchange has been used in a limited number of patients with various success rates. There are only scattered reports of second-line immunotherapy (e.g., tacrolimus, rituximab, and/or cyclophosphamide) in patients with FIRES and AERRPS who improved after other immunotherapies failed.[3,53,66–69] Notably, SE occurring in the setting of autoimmune encephalitis may be refractory to antiepileptic drugs unless the immune mechanism is identified and treated.[70]

Burst-suppression coma is standard care in super-refractory SE. When barbiturates are weaned, however, seizures mostly reappear. In addition, there are concerns regarding its use in FIRES, since prolonged burst-suppression coma has been significantly associated with a worse cognitive outcome. This association should be considered with caution, since longer burst-suppression coma may also reflect a more severe course of the disease.[71,72] Other observational studies from different cohorts of patients with SE have reported poorer outcome associated with anesthetics independent of possible clinical confounders. These results call for caution of inducing burst-suppression coma.[73] A recent retrospective study of refractory SE has shown that midazolam has been as efficacious as thiopental but with fewer adverse events, shorter

Table 4 Diagnostic procedures

Obligate
CSF including oligoclonal bands
Search for infectious agents
MRI:
Initial (e.g., high T_2 or FLAIR signal in encephalitis, cortical dysplasia)
During disease course (e.g., edema, hydrocephalus, and/or brain atrophy)
EEG and continuous EEG:
To guide therapeutic intensity
To recognize nonconvulsive status
Shifting focal seizure pattern was most predictive of drug-resistant epilepsy in FIRES[102]
Whereas, EEG seems as a limited diagnostic tool in differentiating epilepsy or encephalopathy in patients with a possible autoimmune etiology from those without[103]
Neuronal antibodies in serum (including VGKC complex antibody-RIA) and CSF (CSF testing is more sensitive and specific)[104]
Thyroid peroxidase antibodies: marker of autoimmunity rather than neurologic disease specific or pathogenic[86]
Metabolic studies
Genetic studies: Mutation screening in *POLG1, SCN1A,* and *PCDH19*[16]
Neuropsychology assessment at least once before discharge from hospital
Facultative
CSF: neopterin, cytokines, and tau protein
Positron emission tomography:
Hypometabolic areas in temporoparietal and orbitofrontal cortices on both sides corresponding to the predominant EEG foci and neuropsychologic deficits involving language, behavior, and memory in FIRES[105]
Hypermetabolism due to inflammation as well as hypometabolism in anti-NMDAR encephalitis[52]
Muscle biopsy: mitochondrial DNA depletion in isolated cases
Liver biopsy: the best means to diagnose mitochondrial disorders[48]
Brain biopsy: in isolated cases, e.g., to exclude an encephalitis or vasculitis[66]

Table 5 Differential diagnoses

Febrile seizures and febrile status epilepticus[106]
Infectious encephalitis: can occur without significant CSF pleocytosis or MRI changes[107]
Limbic encephalitis and other neuronal antibody-associated epileptic encephalopathies[53]
Hashimoto encephalopathy/steroid-responsive encephalopathy associated with Hashimoto thyroiditis[54]
Posterior reversible encephalopathy syndrome
Alpers disease: hepatic mitochondrial DNA depletion by polymerase gamma (*POLG*) 1 mutations affecting the posterior cortex[108]
Acute necrotizing encephalopathy caused by ran binding orotein 2 (*RANP2*) mutations[109]
Acute onset epilepsy triggered by fever in young girls by *PCDH19* mutations[110]
Dravet syndrome[111]
Primary angiitis of the central nervous system in childhood: small vessel angiitis in brain biopsies with 100% CSF abnormalities and mostly elevated ESR, bilateral subcortical gadolinium enhancement in MRI, 100% steroid responsive[112]
Biotin- (and/or thiamin-) responsive basal ganglia disease with *SLC19A3* mutations triggered by febrile illness: early diagnosis is crucial[113,114]
Citrullinemia with elevation of the amino acid citrulline in CSF mimicking encephalitis[115]

Table 6 Therapeutic options during the acute phase of status epilepticus

Mostly effective in a few small case series
Ketogenic diet as soon as possible (i.e., once FIRES is suspected, e.g., from second day of super-refractory SE)[10,17,18] which also can be provided parenterally[19–22]
Cannabidiol (titrated to 25 mg/kg/d)[81]
Often effective in refractory SE
IV megadose phenobarbital therapy ($>$ 10 mg/kg/d) with serum levels $\geq$ 60–100 mg/dL or possibly higher to avoid coma therapy in FIRES and adults[8,23]
IV midazolam at high dose (up to 1.44 mg/kg/h or even higher): high-dose regime not reported in FIRES but in other refractory SE[116,117]
Effective in single case reports and small case series
IV levetiracetam (50–60 mg/kg/d) combined with phenobarbital (peak 57.9–76.1 µl/mL) and potassium bromide (30–36 mg/kg/d)[118]
IV lacosamide[119]
Ketamine[120]
Lidocaine[121]
High-dose lidocaine 6–8 mg/kg/h combined with high-dose oral topiramate up to 15 mg/kg/d and high-dose phenobarbital with serum level 60–80 mg/dL[122]
Lidocaine plus $MgSO_4$[123]
Valproate, levetiracetam, phenytoin, propofol, oxcarbazepine[1]
Inhalational anesthetic agents[124]
Hypothermia at 33°C[125]
IV magnesium[126]
IV magnesium combined with dextromethorphan[127]
Zonisamide[8]
Epilepsy surgery[128]
Tacrolimus: AERRPS with cerebral infiltration,[66] but no effect in a single case with FIRES (personal observation)
Anakinra (brand name Kineret): interleukin-1 receptor antagonist (up to 5 mg/kg twice daily).[98,129–131]
Electroconvulsive therapy[132]
Possibly effective
Rational polytherapy (enteral and parenteral) from the beginning[133]
Probably effective
Close collaboration between neuropediatricians, immunologists, and with a specialized ICU team[134]
Mostly not effective
First-line immunotherapy (steroids, immunoglobulins, and plasma exchange): should be tried in all cases where an immune-mediated mechanism is suspected (steroids and immunoglobulins applied at once if possible)[3,52,71,135,136]
Unclear efficacy
Second-line immunotherapy (e.g., rituximab or cyclophosphamide, or both)[52,67]
Possibly adverse effects
Prolonged burst-suppression coma was associated with poorer outcome in FIRES and therefore should be avoided if any possible[71,72] If burst-suppression coma is inevitable, aggressive attempts to wean as tolerated are suggested.[57]

lengths of intensive care, and better long-term neurological outcome.[74] Phenobarbital at highest doses also has been efficacious with fewer side effects than anesthetics.

In contrast, early KD might optimize both seizure control and cognitive outcome as FIRES appears to be very susceptible to KD.[75] Multiple small case series highlight the potential value of KD as most effective and thus preferred treatment in FIRES, not only in the acute setting but also for long-term management.[10,76,77] It has been discussed that KD may not only has an antiepileptic effect (e.g., through direct inhibition of the postsynaptic excitatory AMPA receptor by decanoic acid provided in medium chain triglyceride KD)[78] but also acts by a possibly anti-inflammatory mechanism,[11,79] a hypothesis that might be of special impact for FIRES. Therefore,

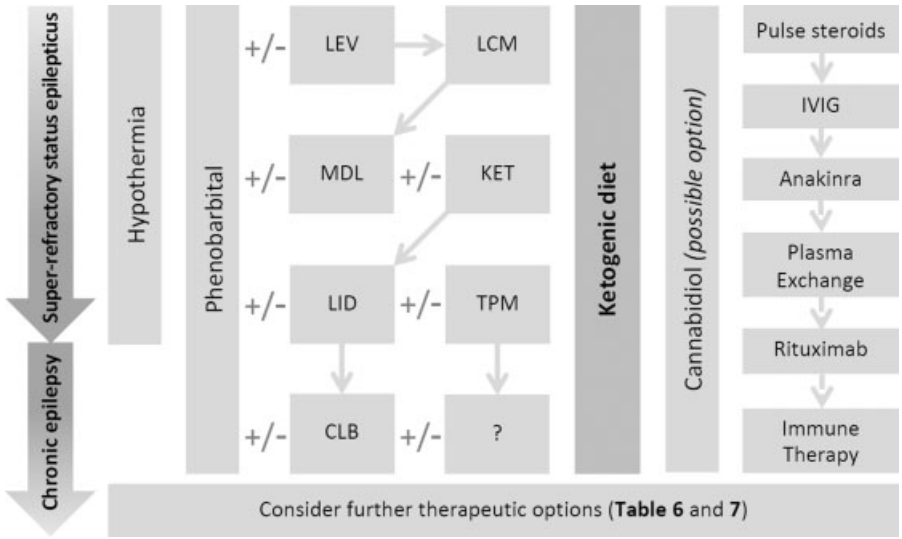

Fig. 4 Proposed treatment flowchart for FIRES (Abbreviations: LEV, levetiracetam; LCM, lacosamide; MDL, midazolam; KET, ketamine; LID, lidocaine; TPM, topiramate; CLB, clobazam; IVIG, intravenous immunoglobulin; +/ − , add if necessary; →, next option).

KD should be considered early in the course of treatment, perhaps even as first-line therapy[17,18] and also by parenteral application[19–22]; though, the combination of KD and propofol may be associated with fatal outcome.[80] Possibly, ketosis by fasting can already be sufficient.

Because, after starting cannabidiol, seizures improved in six of seven children with FIRES, the authors of a recently published open-label case series add cannabidiol as a possible treatment for FIRES in the acute and chronic phases.[81] Further studies are needed.

In summary, we recommend GABAergic therapy at highest doses, immunotherapy, mild hypothermia, KD (also parenterally if necessary) as early as possible, to avoid (especially prolonged) burst-suppression coma, and to test cannabidiol (see ►**Fig. 4**).

Chronic Phase

No systematic study of chronic treatment of FIRES exists. The existing data from a small number of patients show that seizures are mostly very difficult to treat and often require polytherapy that vary from one patient to another (►**Table 7**). Despite polytherapy, severity and frequency of seizures increase periodically and during infections sometimes again resulting in SE. If FIRES is inflammatory mediated, the anti-inflammatory effects of cannabidiol or anakinra may have antiseizure properties especially in the acute but also in the chronic phase of illness.[81–83] Randomized controlled studies are now underway for cannabidiol use in children with highly treatment-resistant epilepsy.[84] Actually, the "network therapy rare epilepsies" (NETRE) retrospectively collects data regarding the effect of perampanel in FIRES.

In summary, the chronic treatment seems not to vary from difficult-to-treat epilepsies due to other causes. Nevertheless, we have noticed that KD, clobazam, phenobarbital, and, potentially in the near future, cannabidiol seems to be the first-line therapy (see ►**Fig. 4**).

Prognosis

If SE persists over weeks despite exhaustion of all available therapeutic options including pharmacologically induced coma and if systemic complications linked to intensive care occur, then the question about prognosis arises. In the largest retrospective multinational study of 77 patients, the outcome of FIRES was predominantly poor.[71] No therapeutic agent was efficacious in shortening the acute phase, with the exception of KD. Approximately 10% died because of intensive care complications or uncontrollable SE. Only one third of the surviving patients had normal or borderline cognitive level (with or without behavioral and learning difficulties), one third had mild-to-moderate mental retardation, and one third had severe mental retardation or were in a vegetative state. Nearly all patients had refractory epilepsy at follow-up. The exact cause of the residual epilepsy is unknown. Multifocal hippocampal and neocortical lesions (neuronal loss, gliosis, and microglial proliferation) seen in one child with AERRPS may be both the result of multifocal seizures during the acute phase and the cause of drug-resistant epilepsy without a latent period afterward.[85] Cognitive levels at follow-up were significantly associated with duration of burst-suppression coma and younger age at onset of FIRES. In summary, outcome seems determined by the underlying pathogenic process and the intensive care treatment during the acute phase.

The chronic phase of FIRES was neither progressive nor regressive. A relapse of the acute phase or a progressive course with cognitive decline (e.g., caused by ongoing bilateral temporal epilepsy or pharmacologic side effects) was exceptional. In this respect, FIRES was monophasic, although to date, complete recovery was also exceptional. The clinical state immediately after the acute phase and early rehabilitation did not change significantly; thus, FIRES was usually irreversible. Notably, as in the acute phase of anti-NMDA receptor encephalitis,[86,87] several children have had

Table 7 Therapeutic options after status epilepticus (*mainly personal observations*)

Effective in several cases
Ketogenic diet (possibly, monotherapy sufficient)
Cannabidiol (titrated to 25 mg/kg/d)[81]
Phenobarbital
Clobazam (also an option during the acute phase)[137]
Partially effective
Valproate
Phenytoin
Lamotrigine (especially indicated, if improvement of behavior is necessary)
Sulthiame
Levetiracetam
Topiramate
Mostly ineffective
Perampanel
Vagal nerve stimulation
Unclear effect
Carbamazepine, oxcarbazepine, or eslicarbazepine
Ineffective
Lacosamide
Only in the rare case of a positive effect in the acute phase
Immunotherapy
Experimental (used for refractory epilepsy)
Thalidomide[138]

prominent speech difficulties and were not talking in the first months of recovery (personal observation).

The chronological evolution of MRI findings may help to estimate prognosis. Evolution of brain atrophy with development of hippocampal sclerosis mostly occurred in a majority of patients already a month after seizure onset, resulting in reduced cognitive level and chronic epilepsy.[61,88] In contrast, we have seen cases with mild intellectual disability and drug-resistant epilepsy despite normal MRI findings. The outcome was very poor if basal ganglia lesions or severe global brain atrophy or both developed in the acute phase resulting in minimal responsive state and increased risk of death because of, for example, respiratory infection in the chronic phase. An intracellular process that is also unknown likely caused the brain atrophy. It may be the results of unremitting SE since this is a cause itself of brain atrophy in animal models.[89,90] Only very few long-term observations, however, exist to date.[91] A systematic follow-up including neuropsychology assessment, for example, as part of a multicenter registry, is necessary.

In the last years, we have the impression, that the outcome was better if KD was used early and if KD was effective. Therefore, the prognosis may improve due to both earlier diagnosis and earlier KD.[77] However, SE may not be influenced despite exhaustion of all available therapeutic options probably reflecting a spectrum of disease severity (personal observation). *Finally, good prognosis despite months of coma has been reported in individual patients.*[92,93]

Future Direction and Tasks

FIRES is an ill-defined epileptic encephalopathy with descriptive term and acronym because of the limited knowledge on its etiology and pathogenesis.[86,94] Because of the rare nature of FIRES, a collaborative network, for example, the "network therapy rare epilepsies" (NETRE), as well as a multinational, preferably web-based, high-quality clinical registry and database seem to be key instruments to develop clinical research, for example, to determine the complete clinical spectrum and the most effective treatment. The latter seems to be most important due to the therapy resistance, up to date. Therefore, alternative therapeutic approaches are urgently needed. For the same reason, prospective studies are needed evaluating whether the diverse therapy successes reported in individual cases are promising or only results of the natural course of the disease.

Based on the favored hypothesis of an immune-mediated pathomechanism, the most promising approaches seem to be genotyping of cytokine-related genes,[95] analysis of proinflammatory cytokines and chemokines in CSF,[40] and measurement of the expression of specific inflammatory molecules known to have a role in seizure mechanisms in brain tissue either obtained as biopsies or postmortem.[27,96] The knowledge in the field highlights new indications for therapy to be considered, for example, the use of drugs already in clinical practice for autoinflammatory or autoimmune diseases[97] such as anakinra.[98]

Due to the rarity and the severity, more multicentric and probably multinational efforts are absolutely essential to improve diagnosis and treatment and to least to clarify the cause of FIRES.

Information and Associations for Families and Careers

www.orpha.net; www.associationparatonnerre.org; FIRES (febrile infection–related epilepsy syndrome): www.facebook.com; www.rarefires.com.

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