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Case Report

Febrile infection-related epilepsy syndromes and their treatment

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Abstract. Acute encephalopathy with inflammation-mediated status epilepticus, followed by the development of medically refractory epilepsy is a spectrum of disorders being increasingly reported in children. Febrile infection-related epilepsy syndrome (FIRES) occurring in school age children and hemiconvulsions, hemiplegia and epilepsy (HHE) syndrome occurring in younger children are the two most commonly recognized entities. The majority of the affected patients develop medically refractory epilepsy and neurocognitive sequelae. We present two illustrative cases and discuss the difficulties faced in their diagnosis and treatment. No specific etiology has been identified and the diagnosis is often made by exclusion. Ketogenic diet has been shown to be effective in controlling the seizures associated with FIRES. Immunomodulating therapies have shown mixed results. Children with HHE developing refractory epilepsy are potential candidates for epilepsy surgery. Urgent research is needed for identifying novel biomarkers as well as for developing therapies targeted at the inflammatory cascade.

Keywords: FIRES, HHE, catastrophic epilepsy, epileptic encephalopathy, ketogenic diet

1. Introduction

There are two epileptic encephalopathy syndromes occurring in children that are characterized by explosive onset of frequent seizures or de novo status epilepticus, frequently associated with a febrile illness, followed by medically refractory epilepsy and neurocognitive sequelae. These syndromes are febrile infection-related epilepsy syndrome (FIRES) and hemiconvulsions, hemiplegia and epilepsy (HHE) syndrome [1]. Recent progress in understanding the inflammatory changes occurring in the central nervous system (CNS) as a cause and consequence of seizures has led to interest in potential treatments targeting these changes in order to better control the epilepsy and limit the development of severe brain injury [2]. We report two illustrative cases and discuss current understanding in the treatment of these epileptic encephalopathies.

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2. FIRES

2.1. Case

A 4-year-old girl presented to the emergency department with acute onset of recurrent seizures. During the preceding wk the child was feeling ill with fever and headache. She was previously healthy, with normal growth and development, and no epilepsy risk factors.

Upon admission to the hospital, she was noted to have seizures with staring and right facial twitching. The seizures subsided briefly after administration of intravenous boluses of lorazepam, but soon recurred. Neurological examination revealed a drowsy patient

who was able to localize painful stimuli. There were no signs of meningeal irritation. The cranial nerves and deep tendon reflexes were normal, although plantar response was extensor bilaterally. The initial electroencephalography (EEG) revealed diffuse slowing of the background activity, but no potentially epileptogenic discharges. She was then empirically treated for presumed meningoencephalitis, as well as status epilepticus.

An extensive evaluation for underlying etiology, including metabolic, infectious, and autoimmune, was unrevealing. The initial magnetic resonance imaging (MRI) scan revealed only subtle hyperintense signal surrounding the fourth ventricle. Brain biopsy, performed on day 20 revealed nonspecific gliosis and diffuse microglial activation. Repeat MRI was consistent with diffuse parenchymal atrophy (Fig. 1).

In spite of aggressive treatment for seizures, the prolonged video EEG monitoring demonstrated clinical and subclinical seizures that were multifocal in onset. Stimulus-induced generalized seizure discharges were also seen on EEG (Fig. 2) [3]. Pentobarbital was started and burst suppression was achieved. However, attempts to wean the pentobarbital resulted in recurrence of seizures. Multiple anti-seizure medications including ketamine were initiated, as well as intravenous immunoglobulin (IVIG) and methylprednisolone. Ultimately, general inhaled anesthesia with isoflurane was required to control seizures. The ketogenic diet (KD) was also started. The status epilepticus persisted for four mo and there were significant neuropsychological sequelae.

Currently, the child is minimally responsive, is tracheostomy and gastrostomy tube dependent, and continues to have multiple seizures per day in spite of being treated with KD and five anti-seizure mediations (Fig. 3).

2.2. Discussion

FIRES is characterized by status epilepticus occurring in a previously healthy child in close temporal proximity to a febrile illness without evidence for CNS infection. Following this acute phase, the disease enters a chronic phase with recurrent daily seizures and severe neurologic sequelae. There is no latent period between the status epilepticus and development of medically refractory epilepsy. The syndrome was initially recognized more than 25 yr ago [4], but has been classified as a distinct electroclinical syndrome only in the last 5 yr. Various terms have been used to describe this epileptic encephalopathy, including devastating epileptic encephalopathy in school-aged children [5], acute encephalitis with refractory repetitive partial seizures [6], FIRES [7,8] and fever induced refractory epileptic encephalopathy of school-age children [1].

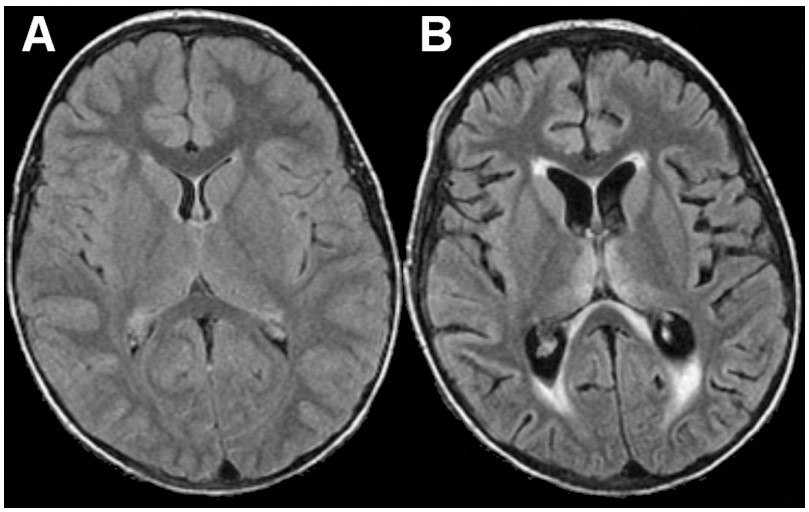

Fig. 1. Magnetic resonance imaging. (A) Axial fluid attenuated inversion recovery image in a child with febrile infection-related epilepsy syndrome on day 1 of hospitalization shows no abnormalities. (B) Axial fluid attenuated inversion recovery image on day 30 of hospitalization shows widening of sulci and lateral ventricles suggestive of diffuse cerebral atrophy. Hyperintense signal changes are seen in bilateral thalami as well as along the ependymal margins of the ventricles and peri-atrial regions.

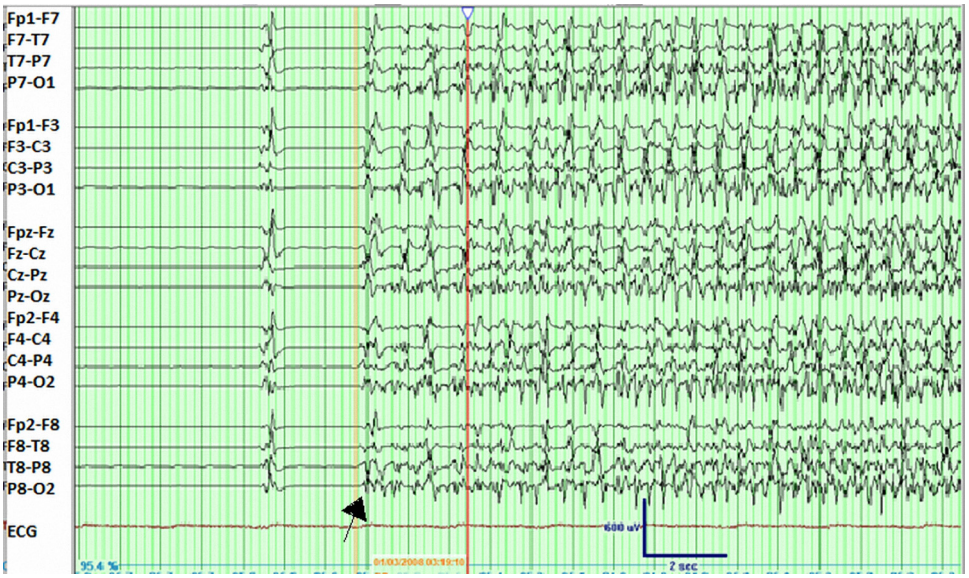

Fig. 2. Electroencephalography on day 17 of hospitalization in the same patient as in Fig. 1, with febrile infection-related epilepsy syndrome, during treatment with pentobarbital for status epilepticus. Electroencephalography background activity shows a burst-suppression pattern. Tactile stimulation (arrowhead) induces a generalized ictal discharge consisting of rhythmic sharp waves, with evolution of frequencies best seen over the posterior head regions (electroencephalography time base is 15 mm/sec).

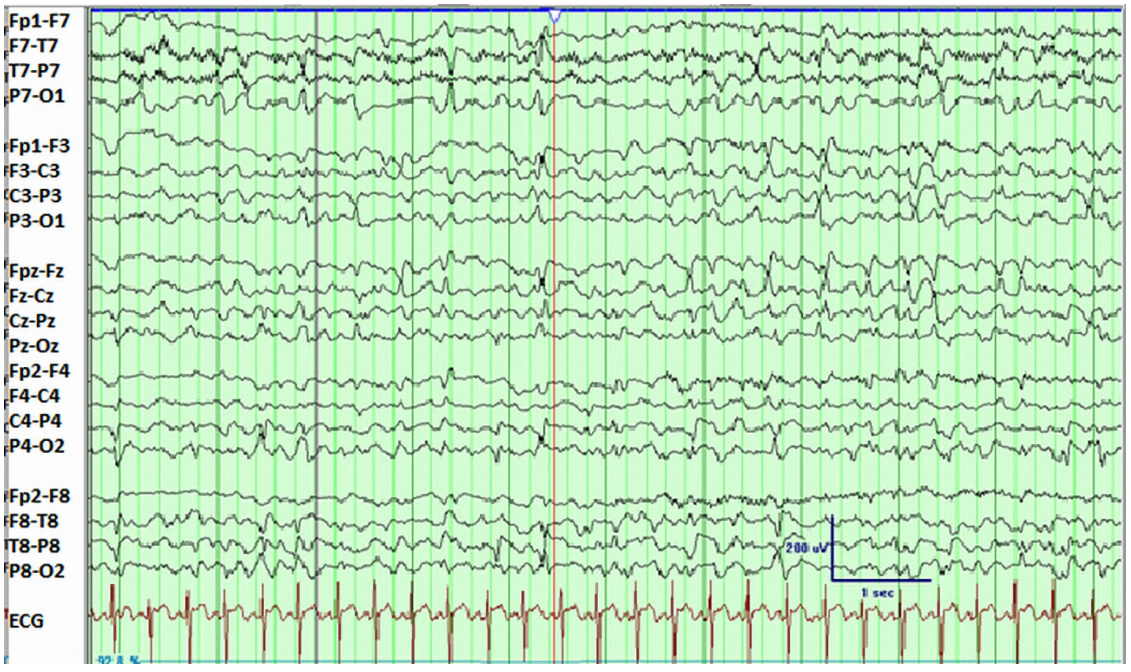

Fig. 3. Electroencephalography done at 3-year follow-up in the same patient as in Figs 1 and 2, with febrile infection-related epilepsy syndrome, shows a diffusely slowed background activity and multifocal epileptiform discharges.

Mechanisms proposed for brain injury include a cycle of inflammation in the CNS leading to seizures, prolonged seizures triggering breakdown of the blood brain barrier, and immune mediated inflammatory responses in the brain [1,9,10].

In a multicenter report of 77 children, 96% of patients had a preceding febrile illness occurring 1-14 d before onset of seizures [11]. The seizures evolved to status epilepticus within 24 h and became refractory to multiple medications. The seizures were typically focal, with and without evolution to bilateral convulsive seizures. The characteristic seizure semiology was described as facial or peribuccal myoclonias. Cerebrospinal fluid studies showed mild to moderate pleocytosis in the majority of patients, but initial cerebrospinal fluid studies showed less than 10 white blood cells. Investigations for infectious and metabolic etiologies were unrevealing. Autoimmune evaluation showed nonspecific abnormalities (oligoclonal bands, anti-GAD antibodies, anti-GluR3) in a minority of patients. MRI was initially normal in the majority of patients. Genetic testing for mutations in SCN1A, POLG1, and PCDH19 in other case studies have also been negative [12].

2.3. Treatment

While there are no known effective treatments for FIRES, many have been tried with some improvement in seizure control. This has included multiple antiseizure medications, lidocaine, paraldehyde, and anesthetic agents to produce a burst-suppression coma [11]. IVIG and steroids have also been tried. The results were disappointing, although IVIG given over 8–9 mo had a beneficial effect in two of eight children in a small series [13]. Vitamin B6, biotin, magnesium, verapamil, dextromethorphan, plasmapheresis, as well as folinic acid treatment have been tried without significant benefit [11]. There has been a reported beneficial effect of therapeutic hypothermia in two children during the acute stage of FIRES after immunomodulatory therapy failed [14]. In the study by Kramer et al. [11], no therapeutic agent was effective in shortening the acute phase, except the KD. KD was used in nine of 77 patients and was effective in seven. Interruption of the diet in one responder was followed by a relapse of intractable status epilepticus with subsequently a fatal outcome. In the other six responders, medically refractory epilepsy developed within a few months.

There are different proposed mechanisms of action for KD including effects on neurotransmitters or their receptors, as well as anti-inflammatory or anti-excitotoxic effects [15,16]. However, there are no evidence based guidelines for the use of KD in FIRES. The KD can be initiated through total parenteral nutrition or enterally via oral intake or gastrostomy tube. Absolute contraindications for KD include metabolic disorders like pyruvate carboxylase deficiency, defects in fatty acid oxidation including carnitine transporter defects and primary carnitine deficiency [17]. Hyperlipidemia and renal stones are relative contraindications for KD [18]. Screening laboratory tests before initiating KD include blood levels of acylcarnitine, lactate, and a fasting lipid profile as well as urinalysis and testing for urine organic acids and calcium/creatinine ratio to ensure these contraindications are not present. Follow-up testing including complete blood count, serum electrolytes including calcium, magnesium, and phosphorus, lipase, selenium, albumin, alkaline phosphatase, 25-hydroxy vitamin D, fasting lipid profile, and beta hydroxybutyrate, as well as urinalysis and urine calcium/creatinine ratio should be done every 3 mo [18].

3. HHE

There are two types of HHE that have been recognized, those with known and those with unknown etiology. Those with known etiology typically have a pre-existing brain disorder such as tuberous sclerosis, Sturge-Weber syndrome or agenesis of the corpus callosum and then develop acute hemiparesis [1]. The present discussion concerns HHE of unknown etiology, which occurs in previously healthy young children.

3.1. Case

A 1-year-old previously healthy infant developed acute onset of seizures and right sided weakness. The child had an upper respiratory tract infection during the preceding week. Upon presentation to the hospital, she was noted to have multiple right sided hemiconvulsive seizures during the first 24 h. Initial EEG showed slowing over the left hemisphere. MRI demonstrated left hemispheric edema with restricted diffusion on diffusion weighted images (DWI) that was not confined to any particular vascular territory (Fig. 4A and B). Investigations for metabolic or infectious etiology were unrevealing. Repeat MRI done 3 wk later showed significant left hemispheric atrophy, predominantly involving the perisylvian and

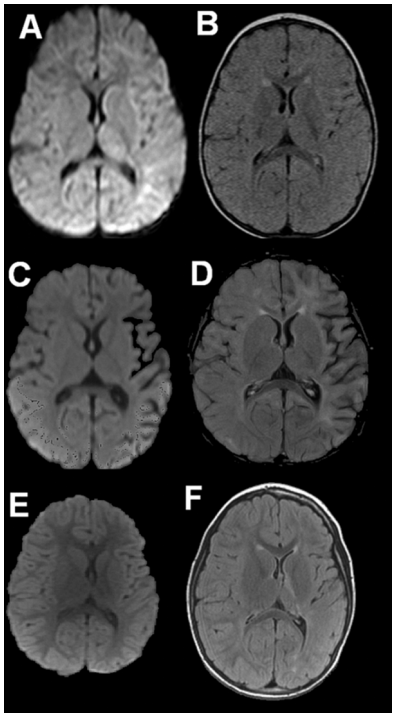

Fig. 4. Magnetic resonance imaging. (A) Axial diffusion-weighted imaging in child with hemiconvulsions, hemiplegia and epilepsy on day 1 of hospitalization shows restricted diffusion in the left hemisphere, resulting in hyperintense signal changes, especially in the thalamus and parieto-temporo-occipital regions. (B) Fluid attenuated inversion recovery images on the same day show subtle increase in signal over the left hemisphere. (C and D). Diffusion-weighted imaging and fluid attenuated inversion recovery images after 3 wk show atrophy of the left hemisphere, especially in the perisylvian regions. (E and F) Diffusion-weighted imaging and fluid attenuated inversion recovery images after 3 yr show a left hemisphere that is smaller than the right.

parieto-occipital regions (Fig 4C and D). Brain imaging at 3 yr showed a left hemisphere that was smaller than the right, but no new signal abnormalities (Fig. 4E and F).

When she presented for a comprehensive evaluation for epilepsy at age 5 yr, she had partial recovery of her right hemiparesis, but did have cognitive and behavioral sequelae. She also continued to have recurrent daily unprovoked seizures in spite of being treated with multiple anti-seizure medications. Habitual seizures were recorded and all arose from the left hemisphere (Figs 5 and 6).

3.2. Discussion

The HHE syndrome was first described by Gastaut et al. [19] in 1960, although its etiology remains unclear [20–23]. It has been classified along with FIRES [24] and new-onset refractory status epilepticus [25] under the rubric of an inflammation-mediated epileptic encephalopathy [1]. HHE typically presents with fever-associated prolonged hemiconvulsions followed by a flaccid hemiplegia that progressively becomes spastic. The chronic phase develops after a variable period of seizure freedom lasting months to years. Two thirds of patients subsequently develop medically refractory epilepsy. In a small percentage of patients, the motor deficit can resolve. The cognitive and language outcome can vary, depending on the extent of brain injury as well as the involvement of the language dominant hemisphere. Its prevalence and incidence is unknown, but the incidence is reportedly decreasing in developed countries due to advances in the emergency treatment of status epilepticus [21,26].

The MRI in the acute phase of HHE shows restricted diffusion in the affected hemisphere that is not confined to a particular vascular territory [27]. This is then followed by ipsilateral brain atrophy [26]. Pathologic studies during the acute phase demonstrate laminar necrosis and edema of the cortex without evidence for inflammation. After atrophy occurs, pathology demonstrates a cortical laminar scar and diffuse secondary demyelination [28].

Differential diagnoses for HHE include Todd's paresis, stroke, CNS infections, acute disseminated encephalomyelitis, traumatic brain injury, metabolic and mitochondrial disorders, as well as developmental brain malformations [29,30]. HHE can be readily differentiated from seizures related to stroke because the latter typically occur after the onset of the motor deficit. This syndrome also must be differentiated from Rasmussen's encephalitis in which focal seizures and epilepsia partialis continua occur for many wk or mo followed by gradual onset of ipsilateral hemiparesis.

3.3. Treatment

The treatment during the acute phase of the illness is mainly supportive, with antipyretic and anticonvulsive medications. Though there are no evidence-based treatment guidelines available for the treatment of HHE, it has been proposed that early treatment of cerebral edema with anti-edema agents and the use of the N-methyl-D-aspartate receptor antagonists to limit excitotoxic neuronal damage during the acute period could help to limit brain injury [31]. It is not known

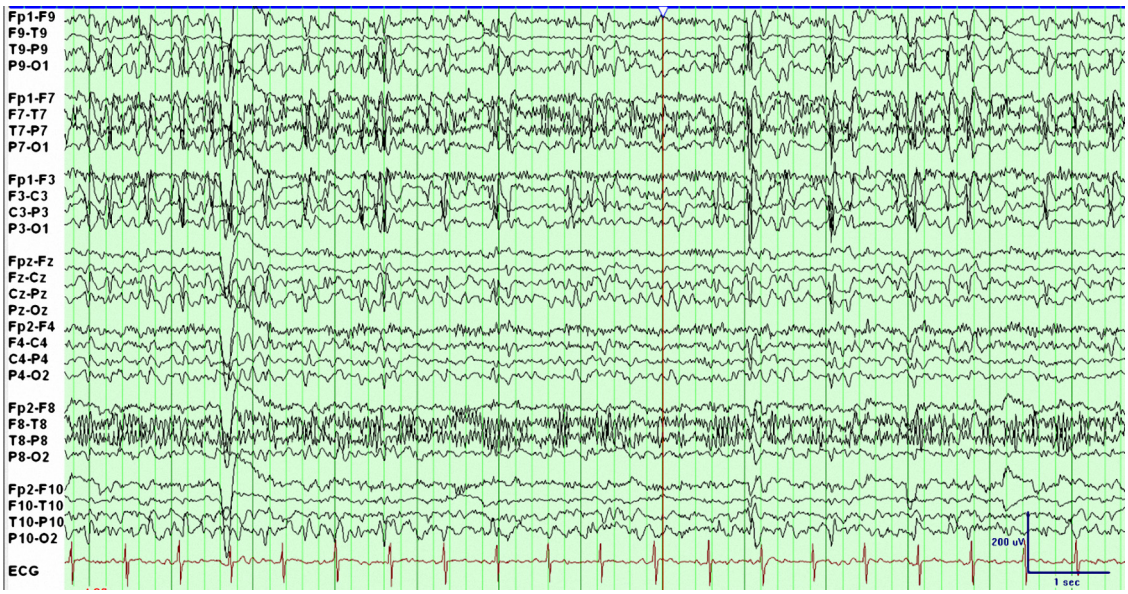

Fig. 5. Interictal electroencephalography in the same child as in Fig. 4 with hemiconvulsions, hemiplegia and epilepsy, at the age of 5 yr, shows an asymmetric slowing of the background activity over the left hemisphere. Frequent sharp waves are seen over the left temporal and left fronto-central and parietal regions, at times synchronously involving the right side.

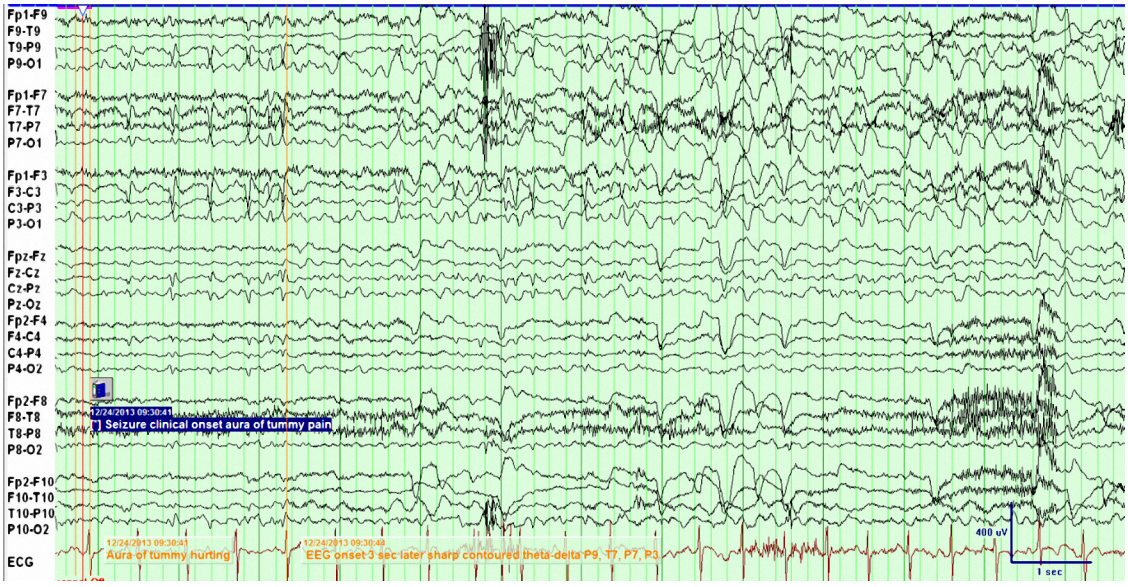

Fig. 6. Ictal electroencephalography in the same child as in Fig. 4 and 5 with hemiconvulsions, hemiplegia and epilepsy, at the age of 5 yr, shows seizure-onset over the left hemisphere with rhythmic theta and delta frequency activity, maximum over the temporal region.

if using antiepileptic medications in children with HHE syndrome beyond the acute phase helps to prevent remote seizures and epilepsy. Physical and occupational therapy has an important role during the acute and chronic periods and helps in maximizing motor function [29].

There is evidence that surgical treatment of medically refractory epilepsy in the chronic phase in HHE syndrome is beneficial [32]. The choice of surgical procedure is determined by the results of the presurgical evaluation. Patients developing temporal lobe epilepsy could have excellent seizure outcome

after anterior temporal lobectomy. Patients developing neocortical/multifocal epilepsy could be candidates for procedures such as multilobar resections, functional hemispherectomy or corpus callosotomy and tend to have a less favorable seizure outcome [32].

4. Conclusions and future perspectives

The majority of the treatments currently used for acute encephalopathy with inflammation-mediated status epilepticus show only partial efficacy. There is some evidence suggesting that KD could be useful in treating acute status epilepticus and medically refractory epilepsy in patients with FIRES [11]. Discovery of biomarkers is necessary for these conditions so that early diagnosis and initiation of appropriate treatment can occur [33]. Treatment strategies including neuroprotection, such as therapeutic hypothermia, should be explored [14]. Clinical trials of novel drugs targeting specific stages of the inflammatory response cascade are urgently needed [34,35].

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