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Original Article

Chronological Evolution of Magnetic Resonance Imaging Findings in Children With Febrile Infection-Related Epilepsy Syndrome

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ABSTRACT

OBJECTIVE: To describe and analyze the chronological evolution of the radiological findings in seven children with febrile infection-related epilepsy syndrome. **METHODS:** This is a retrospective study describing the radiological findings and evolution in seven children with febrile infection-related epilepsy syndrome who presented from 2009 to 2013. The children all fit the defined clinical criteria for febrile infection-related epilepsy syndrome; all had a history of normal psychomotor development who presented with acute-onset catastrophic partial status epilepticus associated with a febrile illness or unspecific infectious process. The children were identified from the author's weekly review of the pediatric inpatient service, and then the data were collected and analyzed retrospectively. **RESULTS:** Six males and one female ranging from 3 months to 9 years of age presented with status epilepticus preceded by a febrile illness. Extensive investigations for infectious, autoimmune, and metabolic etiologies were unremarkable. Multiple antiepileptic medications were attempted, including drug-induced coma in all of them, with poor response. Immunotherapy with intravenous steroids or intravenous immunoglobulin (three patients had both) was tried in six of seven patients with a poor response. Ketogenic diet was initiated in four of seven patients with limited response. Serial magnetic resonance imaging studies, done from the initial presentation through 18 months of follow-up, showed evolution from normal imaging to severe cerebral atrophy. Progressive cytotoxic edema involving mostly bilateral hippocampi and temporal lobes was appreciated in one to three weeks. At one month from seizure onset, mild to moderate cerebral atrophy and hippocampal sclerosis was appreciated that continued to progress over the next year. After six to twelve months, most of the patients showed moderate to severe cerebral atrophy and by one year, cerebellar atrophy was also appreciated. **CONCLUSION:** Febrile infection-related epilepsy syndrome is a devastating epilepsy syndrome of childhood without a diagnostic biologic marker. The magnetic resonance imaging findings appear to be progressive and typical. Thus, combined with the clinical course, imaging findings can help to confirm the diagnosis (until a biologic marker is found). This hopefully will allow multicentered treatment protocols in the future.

Keywords: refractory status epilepticus, FIRES, fever, children, hippocampal sclerosis

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Introduction

Febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy with refractory status epilepticus and a yet undefined etiology.[1]

Multiple cases and case series have been reported in the literature of children and adults who developed refractory partial status epilepticus related to an encephalitis due to an unidentified agent or immune encephalopathy.[1-9]

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Several different names have been suggested for this entity. Some of these names include severe refractory status epilepticus due to presumed encephalitis,[3] idiopathic catastrophic epileptic encephalopathy,[4] new-onset refractory status epilepticus,[5] severe refractory status epilepticus owing to presume encephalitis,[6] devastating epilepsy in school-age children,[7] acute encephalitis with refractory repetitive partial seizures,[8] and fever-induced refractory epileptic encephalopathy syndrome.[9] By whatever name, these entities share common clinical characteristics, including a known febrile infection preceding the onset of refractory status epilepticus and the absence of any identified infectious agent.[1-9] In 2011, it was proposed that these conditions represent the same clinical entity.[10]

FIRES can be defined by the common clinical characteristics seen in all these patients, including a recent history of a febrile infection or unspecific illness preceding the initiation of acute refractory partial status epilepticus in the absence of any identified infectious agent or autoimmune process.[1,9,11]

Autoimmunity,[9] genetic predisposition, and an inflammation-mediated processes[12,13] have been proposed as possible pathophysiologic mechanisms, but the etiology remains unknown. Neuroimaging performed during the acute phase of FIRES is often normal.[1,14] Hyperintense lesions on magnetic resonance imaging (MRI) involve predominantly the temporal regions, the insulae, and the basal ganglia during the acute phase[1,3,7,9,14] and may be secondary to long-lasting epileptic activity.[1] During the chronic phase, global brain atrophy has been documented.[1,14]

We described the MRI findings and chronological evolution of seven children with FIRES. We believe these findings are characteristic enough to assist the clinician in identification of this uncommon epilepsy syndrome.

Methods

Subjects

This is a retrospective analysis performed at Le Bonheur Children's Hospital in Memphis, Tennessee, of seven children with FIRES who presented from 2009 to 2013. We reviewed inpatient admissions on a weekly basis; suspected cases were tabulated and then reviewed in a retrospective manner. We review the clinical presentation, hospital course, and diagnostic studies, including cerebrospinal fluid (CSF) findings and infectious, metabolic, and autoimmune investigations. Different treatment methods including antiepileptic drugs (AEDs), first cycle of medically induced burst suppression, hypothermia, immunotherapy, and ketogenic diet given during the acute phase were reviewed. The MRI findings from presentation up to 60 weeks from disease onset were described.

The inclusion criteria included previously healthy children with normal psychomotor development, acute-onset catastrophic partial status epilepticus associated with recent febrile illness or infectious process, no infectious pathogen identified on testing of CSF, serum, or any other body fluid; negative metabolic and autoantibody evaluations; and evolution to chronic refractory epilepsy.[1] Refractory status epilepticus was defined as a seizure lasting longer than 30 minutes or a series of seizures without return to baseline level of alertness between seizures and that persisted despite treatment with adequate doses of two or three anticonvulsants.[15] Acute-onset catastrophic status epilepticus was defined as continuation of seizures following the first cycle of burst-suppression coma.[1]

Magnetic resonance imaging

Most of the imaging studies were performed at our facility, and the others were obtained from outside facilities. One neuroradiologist evaluated all the images, describing and confirming the MRI findings.

Results

Clinical presentation and investigations

We included a total of seven patients, six males and one female. All were previously healthy with normal development, with no history of chronic medical condition or previous history of seizures.

The median age at onset of FIRES was 4.7 years (range 3 months to 9 years) (Table 1). All patients exhibited a nonspecific illness before the status epilepticus. All of the children were febrile and most often experienced signs of upper respiratory tract infection and, less frequently, gastroenteritis. The nonspecific illness preceded the onset of seizures with a median duration of 5.4 days (range 1-14 days).

All patients presented with complex partial seizures. Shortly after the onset of seizures, the seizures rapidly exacerbated into status epilepticus, 71.4% in less than 24 hours. Electroencephalography (EEG) in all the patients showed partial-onset seizures of independent fronto-temporal origin. Interictal, multifocal epileptiform discharges were reported in 42% of the patients, predominantly over the temporal head regions, and 68% showed temporal lobe epileptiform discharges only.

CSF analysis was performed in all patients, and mild pleocytosis (mean leukocyte count 10) was found in three (42.9%), who also had associated elevated CSF protein (range 52-89 mg/dL). All patients underwent a thorough investigation for infectious agents, including polymerase chain reaction (PCR) for herpes simplex 1 and 2. In addition, some of the patients had PCR performed for enterovirus, which was uniformly negative. Antibodies were tested for West Nile virus, St. Louis encephalitis virus, Epstein-Barr virus, influenza A-B, parainfluenza, adenovirus, arbovirus, respiratory syncytial virus, and human metapneumovirus. Respiratory syncytial virus, adenovirus, influenza A and B virus, and parainfluenza were also tested by nasopharyngeal swab. In addition, serology was performed for *Borrelia burgdorferi*, *Bartonella*, and rickettsia. All tests were negative except for two patients who presented positive IgM titers for mycoplasma in blood with negative CSF studies and one with positive serum IgG and negative CSF studies (no active central nervous system infection was suspected for either).

Most patients had a metabolic evaluation that included blood carnitine profile, ammonia, pH, lactic acid, serum amino acids, and vitamin B_6 and B_{12} levels. CSF analysis for lactic acid, pyruvate, and amino acids was also performed in some of the patients. Finally, genetic testing for ARX and SCN1A genes and mitochondrial sequencing including POLG1, SUCLA1, DGUOK, and TK2 were performed. These tests were negative in all patients.

Autoantibody tests were performed in the search for autoimmune neurological disease, and all were negative (four patients were assayed for anti–*N*-methyl-D-aspartate receptor antibodies, and three of these four