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Febrile infection-related epilepsy syndrome: A study of 12 patients

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ABSTRACT

Purpose: To analyze the electroclinical features, neuroimaging findings, treatment, and outcome of 12 patients with febrile infection-related epilepsy syndrome (FIRES).
Methods: This is a retrospective study of 12 children with FIRES with a mean time of follow-up of 6.5 years carried out at the Garrahan Hospital of Buenos Aires between 1997 and 2012.
Results: Eight males and four females had focal status epilepticus preceded by febrile infection with a mean age at presentation of 8.5 years. In the acute period, the treatment included antiepileptic drugs (AEDs) in all cases, immunotherapy in 10 cases, and burst-suppression coma in eight. The ketogenic diet was tried in two, plasmapheresis in one, and rituximab in one. Two patients treated with IVIG and one patient given steroids had a good response, but in this phase only three patients had a prolonged good response to IVIG and a ketogenic diet. No patients died in this period. In the chronic epilepsy phase, all children had seizures arising from neocortical regions. All patients had refractory epilepsy, and most mental retardation, and behavioral disturbances. All received different AEDs and in this phase a third patient was put on a ketogenic diet. One patient was operated without good results. Only two cases had a good outcome after 2 and 10 years of follow-up.
Conclusion: FIRES is a well-defined severe epileptic syndrome, probably in the group of epileptic encephalopathies, characterized by focal or multifocal seizures arising from the neocortical regions with an unknown etiology. Immunoglobulin and the ketogenic diet may be considered a potentially efficacious treatment.

1. Introduction

Febrile infection-related epilepsy syndrome (FIRES) is considered a severe epileptic encephalopathy with multifocal refractory status epilepticus.[1]

In 1986 Awaya and Fukuyama first described an encephalitis-like entity occurring in previously normal children.[2] Since then, the syndrome has been variably called severe refractory status epilepticus due to presumed encephalitis,[3] idiopathic catastrophic epileptic encephalopathy,[4] new-onset refractory status epilepticus,[5] devastating epileptic encephalopathy in school-aged children,[1] acute encephalitis with refractory repetitive partial seizures,[6] febrile infection-related epilepsy syndrome,[7] and fever-induced refractory epileptic encephalopathy in school-age children.[8]

FIRES in previously healthy children is characterized by three phases: An initial phase with a simple febrile infection, a few days later followed by an acute phase with highly recurrent focal seizures that evolve rapidly into refractory status epilepticus often with no more fever and generally without additional neurological features, and finally a chronic phase consisting of drug-resistant epilepsy and neuropsychological impairment.[7] These symptoms occur mostly in children between 3 and 15 years of age, but adult patients have also been described.

Series of patients with this particular epileptic encephalopathy have been published in Japan, the UK, France, Germany, Italy, the US, Austria, Singapore, and Taiwan.[1,4–10]

The etiology and the mechanisms underlying of FIRES are still unknown, and an immunologic source,[7,10–14] a genetic predisposition, and an inflammation-mediated process[11] have been hypothesized. Currently, the ketogenic diet may be considered as an efficacious treatment.[8]

Here, we analyze the electroclinical features, neuroimaging findings, treatment, and outcome of 12 patients with FIRES.

2. Methods

This is a retrospective study conducted at the Garrahan Hospital of Buenos Aires of 12 children with FIRES seen between 1997 and

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2012. We evaluated the charts of these patients with a mean time of follow-up of 6.5 years (range, 1–15 years).

The inclusion criteria were the following: Previously healthy children between 2 and 16 years of age with normal psychomotor development, acute onset of refractory seizures associated with an encephalitis-like illness; no infectious pathogen found on testing of cerebrospinal fluid (CSF), serum, or other body fluids; and evolution to chronic epilepsy without an anticonvulsant-free latent period.[8] The status was considered refractory if it failed to respond to initial antiepilepic drug treatment (intravenous benzodiazepines, phenytoin, phenobarbital, as well as valproic acid and levetiracetam).

Patients with a similar presentation due to viral encephalitis, acute disseminated encephalomyelitis, Rasmussen encephalitis, structural brain abnormalities, or metabolic disorders were excluded.

Based on the medical records we evaluated personal antecedents, family history, and clinical details including seizure semiology and management in the acute period. Virological, immunological, metabolic, and genetic investigations were studied. Neuropsychological assessments as well as clinical features and management of the chronic epilepsy were also analyzed.

All patients had CSF, blood, and other body fluids tested for infective pathogens. In all cases markers of inflammation in CSF and blood were investigated. Different antibody and metabolic tests were performed. Genetic testing and brain biopsy were not performed in any of the patients.

All interictal and ictal EEG recordings, computerized tomography (CT) scans, and magnetic resonance imaging (MRI) performed in both the acute and chronic phases were analyzed. Six and four patients had video-EEG recordings in the acute and chronic phases, respectively. All patients underwent MRI study at 1.5 T in the acute period and in the chronic phase, and three of them at 3 T with an epilepsy protocol in the chronic period. Positron emission tomography scans were not done in any of the patients in either acute or chronic phases.

In the chronic phase, we analyzed the electroclinical features, treatment, and evolution. Behavior was assessed by parental report. The neuropsychological evaluation included standardized tests of intellectual abilities in all patients.

3. Results

3.1. General features

We included 12 patients, eight males and four females. All were previously well, with a normal development. No patients had remarkable personal antecedents or a past history of seizures. One patient had a family history of febrile seizures and another had a family history of epilepsy.

3.2. Clinical and EEG presentation

The children had a mean and median age at presentation of 8.5 and 10 years (range, 2–13.5 years), respectively. Upper respiratory tract infection and gastroenteritis, both associated with fever, were observed in nine and three patients, respectively. Clinical encephalitis-like features characterized by fever, headache, drowsiness, and confusion preceded the onset of seizures by 2–10 days.

In the acute phase, the seizures were focal with loss of consciousness in all children, and with secondary generalization characterized by bilateral clonic seizures in three. Autonomic manifestations, such as pallor, apnea, and cyanosis, were registered in eight patients. Three patients also had apparently generalized seizures. The seizures rapidly increased in frequency (28–102 seizures daily) and exacerbated into status epilepticus within 24–36 h. One patient had repetitive facial myoclonias. The duration of intensive care treatment was 2–40 days (median 16 days).

Interictal EEG recordings showed diffuse delta–theta background slowing was seen in all cases. The initial ictal EEG recordings showed a temporal seizure onset in four children (33%), frontotemporal in four (33%), frontal in two (16.5%), and frontoparietal in two children (16.5%) (Fig. 1). All of them rapidly developed multifocal and independent seizures, unilateral or

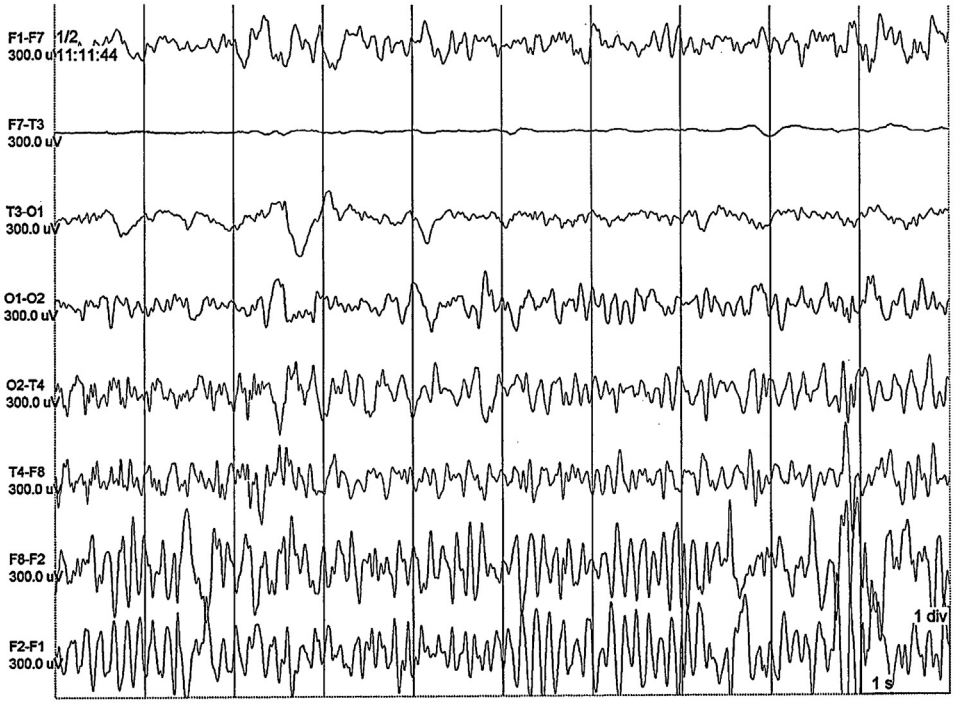

Fig. 1. Ictal EEG recording shows rhythmic theta activities predominantly in the right frontal lobe associated with left focal orofacial clonic seizures.