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CASE REPORT

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Hippocampal Changes in Febrile Infection-Related Epilepsy Syndrome (FIRES)

Amit Agarwal[1E], Shyamsunder Sabat[1E], Krishnamurthy Thamburaj[1E], Sangam Kanekar[2E]

[1] Department of Radiology, Penn State University, Hershey, PA, U.S.A.
[2] Department of Radiology and Neurology, Penn State University, Hershey, PA, U.S.A.

Author's address: Amit Agarwal, Department of Radiology, Penn State University, 500 University Drive, Hershey, PA-17036, U.S.A., e-mail: amitmamc@gmail.com

Summary

Background: Febrile seizures are the most common seizure disorder in childhood, associated with a significant rise in body temperature. However, post-infectious refractory afebrile form of seizures in previously healthy children is being increasingly recognized in around the world, which evolves into a chronic refractory form of epilepsy. The term 'Febrile infection-related epilepsy syndrome' (FIRES) has been proposed for these conditions and represents a refractory severe post-infectious epileptic condition in previously normal children.

Case Report: We report the initial and follow-up MR imaging findings in a 5year-old with refractory epilepsy post-febrile seizures.

Conclusions: In summary, acute post-infectious seizures are increasingly being recognized across the globe with the newly coined term 'Febrile infection-related epilepsy syndrome'(FIRES) for this group of immune-mediated epileptic encephalopathy in previously healthy children. This has three phases: episode of simple febrile infection, followed by acute refractory seizures and lastly the chronic phase of neuropsychological impairments and seizures.

MeSH Keywords: Hippocampus • Magnetic Resonance Imaging • Seizures

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Background

Febrile seizures are a common cause of convulsions in young children seen in response to fever, excluding any causes of central nervous system infection. Recently, clinical entities, characterized by severe epilepsy with afebrile, acute or sub-acute onset, have been described, sometimes associated with status epilepticus. These are severe epileptic entities in previously normal children, preceded by fever associated with common infections. They eventually progress into chronic refractory epilepsy, with no silent period, secondary to underlying immune-mediating or inflammatory process. We describe the initial and follow-up MRI findings in a young child presenting with status epilepticus, three weeks after fever related to upper respiratory tract infection, who eventually developed chronic refractory epilepsy. Most of the researchers have concluded that damage to the medial temporal cortex is the underlying cause for this refractory epileptic condition.

Case Report

A four-year-old child was found on the floor with a right-sided gaze deviation and tremulousness. The father called 911 and the child was taken to a nearby community hospital where he received Lorazepam and Fosphenytoin. The seizure continued. A CT scan of the head done subsequently was unremarkable. Since the seizure did not stop, the child was transferred to our University Medical Center. The seizure stopped after around 3 hours. Subsequent, neurological examination was unremarkable, except for mildly decreased tone in the lower extremities. The child had no significant prior medical history except for sinus infection around 3 weeks back and was having fevers off and on. MR examination, done on the same day, revealed increased T2 signal and edema involving the right hippocampus (Figure 1) with no pathological contrast enhancement. Radiological differential included encephalitis and post-ictal changes. The latter was felt to be less likely given the

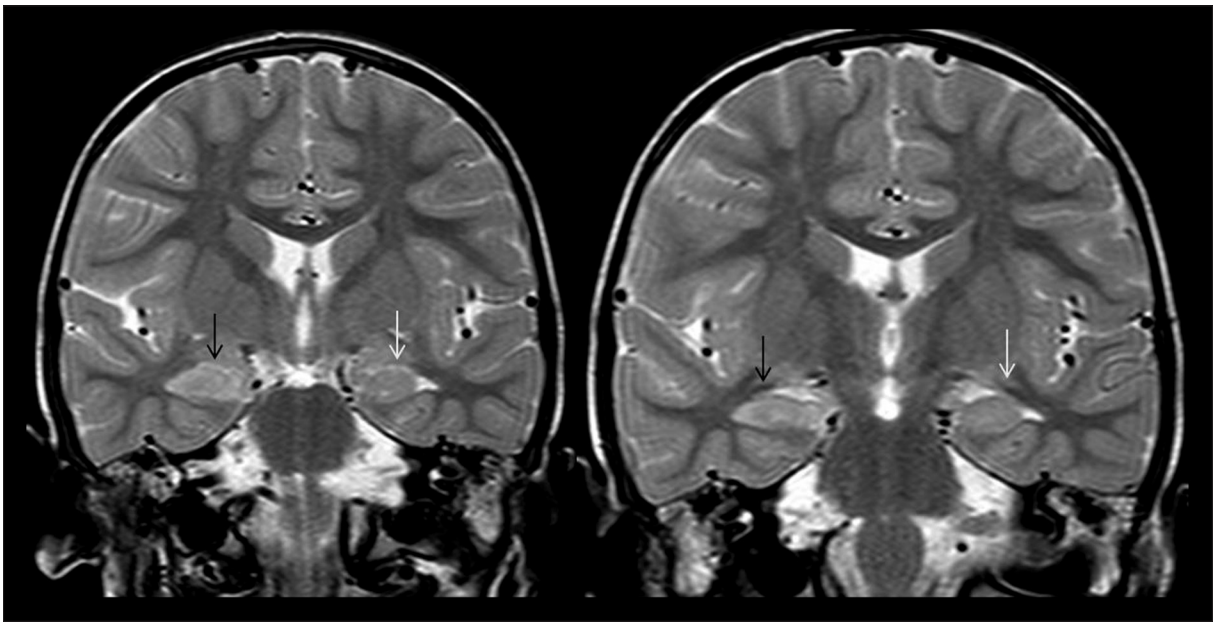

Figure 1. MR examination done within 24 hours of status epilepticus. Contiguous T2 images reveal swelling and increased T2 signal of the right hippocampus (*black arrows*). The left hippocampus (*white arrows*) shows normal morphology and signal pattern.

isolated involvement of the hippocampus. Viral encephalitis was later ruled out clinically given the absence of fever and an unremarkable lumbar tap. Multifocal epileptiform discharges were recorded in the frontotemporal region on the interictal EEG performed on the second day. The patient was started on Keppra (200 mg b.i.d) and discharged on the third day with no other seizure activity noted in the interim. Over the following months the patient had multiple episodes of self-limiting seizures with frequent hospitalizations. The seizures were refractory with poor response to antiepileptic drugs. Multiple lumbar taps during the course were unremarkable. Interictal EEG obtained twice over a period of 6 months showed generalized epilepiform changes, with predominantly right frontal and temporal origin. No ictal EEG was obtained. Multiple MRI studies of the brain were obtained during that course. Images obtained around 7 months after the initial presentation showed signal changes and atrophy of the right hippocampus along with mild global parenchymal volume loss (Figure 2). There was no recurrence of status epilepticus. The child showed significant cognitive decline over that period.

Discussion

Febrile seizures (FS) are common, affecting 2–5% of children by 6 years of age, and are associated with an increased risk of subsequent epilepsy. Epilepsy develops in 2–4% of children with a history of FS, four times more frequently than in children without FS [1]. Prolonged febrile convulsion (PFC), defined as a seizure lasting at least 30 min associated with fever and not of neurological origin, is the most frequent type of convulsive status epilepticus in children under the age of 5 years and, although the outcome is largely perceived to be excellent, there is a longstanding debate on whether PFC can cause mesial temporal sclerosis (MTS). There are very few reports of patients with PFC developing acute hippocampal edema that progresses to hippocampal atrophy within several months of the acute event [2]. Recently, there have been many case reports of post-infectious epilepsy in the pediatric age group, in different parts of the world [3]. Awaya and Fukuyama in 1986 first reported this clinical entity of epilepsy with sudden onset, following encephalitis-like condition in a previously healthy child [4]. Many subsequent papers across the world reported a similar condition of epilepsy of unknown etiology in children without any underlying metabolic, structural or genetic disease [5]. Different terms have been coined for this condition, including 'devastating epileptic encephalopathy in school-aged children', 'acute encephalitis with refractory repetitive partial seizures ', and 'febrile infection-related epilepsy syndrome (FIRES)' (Baalen et al., 2010) [3]. These names suggest infectious etiology and acute presentation of epileptic encephalopathy. Acute onset of presentation in febrile patients with mild increase in white blood cell count on CSF lead the authors to suggest an underlying viral or immune-mediated condition. However, no infective organism was identified in a complete CSF analysis. Post-mortem or biopsy in a few of the reported cased failed to document histological findings of inflammation [5]. Typically, FIRES has an acute phase with progression into a chronic refractory form and absence of a silent period. Although there is no established criterion, the diagnosis of FIRES is usually made in previously healthy children with (a) acute onset of seizures following a febrile illness (b) absence of any infectious pathogen in CSF or serum, and (c) progression into chronic refractory epilepsy. The acute phase is described in detail in many of these reports. However, the features of the chronic epileptic phase are poorly documented. Previously healthy children present with febrile illness, mental status changes, and varying forms of acute-onset seizures, giving a clinical encephalitis-like picture. The seizure episodes show a poor response to a variety of anti-epileptics. This then rapidly progresses into status epilepticus which requires more intensive care and management. There is gradual progression into a chronic refractory epileptic condition without

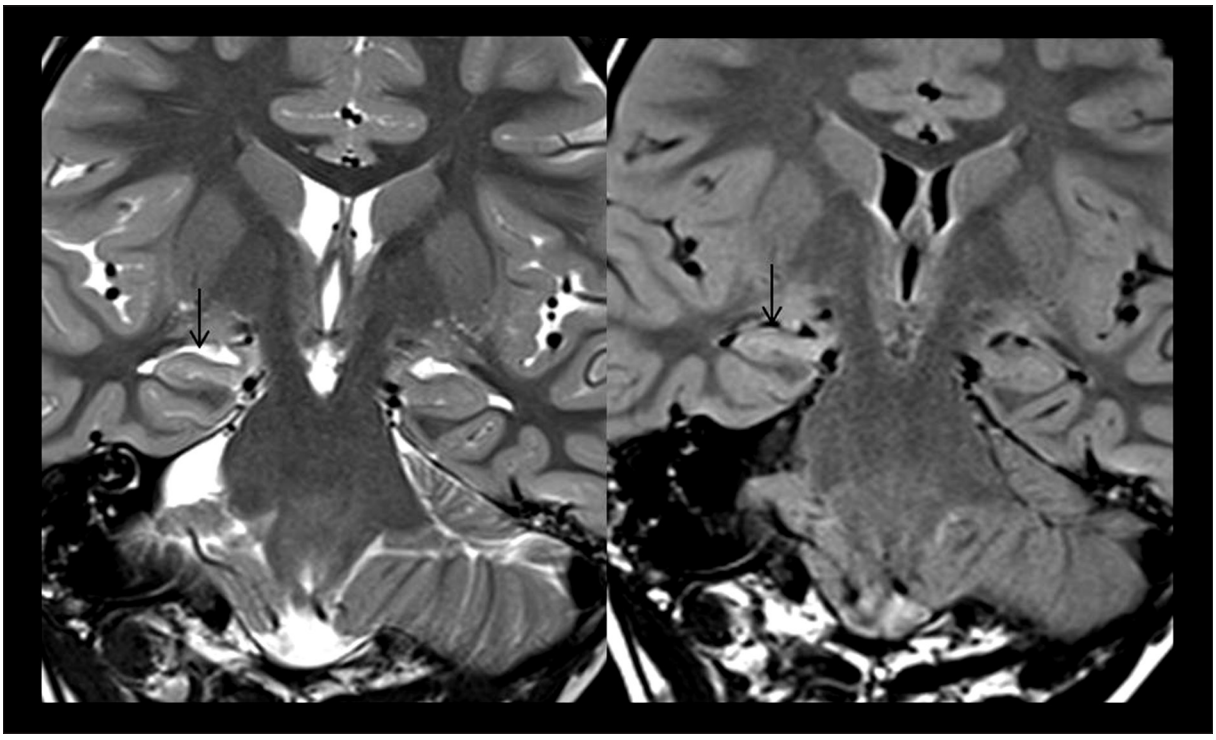

Figure 2. Follow-up MR examination done 7 months after status epilepticus. Coronal T2 and FLAIR images show volume loss (atrophy) and increased T2 signal of the right hippocampus (*black arrows*). The left hippocampus shows normal architecture, normal volume and signal pattern.

an intervening uneventful period. Besides refractory seizures, cognitive decline and behavioral changes have been reported in many of these patients [6]. There is very little literature describing the imaging findings in these patients with acute post-infectious epilepsy. In one of the major series by Baalen et al. (2010), MR examination of the brain was unremarkable during the acute phase in around 41% of children [3]. A similar proportion of children (41%) however did show signal changes or edema in the hippocampal and medial temporal region. Brain MRI during the chronic stage of the disease is usually unremarkable or may show focal areas of cortical atrophy. Few patients show hippocampal atrophy or signal changes. Our patient had acute unilateral hippocampal edema which gradually progressed on to hippocampal atrophy over a period of 7 months. There are not many differential diagnoses. Patients with generalized tonic seizures, status epilepticus or any other acute epileptic condition can show post-ictal changes on MRI of the brain. Imaging findings include transient multifocal areas of swelling and T2 signal changes involving the cortex and subcortical white matter with or without restricted diffusion. However, these changes are classically located in the frontal and parietal lobes. The progressive nature and characteristic locations of the signal changes in our patient ruled out the possibility of other structural lesions [7]. Treatment options are limited and patients usually progress into adulthood with epilepsy. No antiepileptic has been useful in these patients on a long-term basis and surgery is not recommended given the potentially diffuse cortical characteristic of seizures. Vagal nerve stimulators and ketogenic diet are the most commonly used treatment options with variable results.

Conclusions

In summary, acute post-infectious seizures are being increasingly recognized across the globe with the newly coined term 'Febrile infection-related epilepsy syndrome' (FIRES) for this group of immune-mediated epileptic encephalopathy in previously healthy children. This has three phases: episode of a simple febrile infection followed by an afebrile phase with acute onset of refractory seizures or status epilepticus showing poor response to medications, and lastly the chronic phase which includes refractory seizures, cognitive decline and behavioral problems. Acute hippocampal edema may be observed in a wide proportion of these patients which may be reversible or more likely progress to hippocampal atrophy.

Conflict of interest

The authors declare that they have no conflict of interest.

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