Neurological Sciences (2019) 40:2407–2410
https://doi.org/10.1007/s10072-019-03925-0

LETTER TO THE EDITOR

Febrile infection-related epilepsy syndrome (FIRES) in an adult patient: an early neuroradiological finding

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Received: 11 February 2019 / Accepted: 7 May 2019 / Published online: 16 May 2019

Dear Editor,

New onset refractory status epilepticus (NORSE) is a clinical presentation in a patient without active epilepsy or other pre-existing relevant neurological disorders, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause [1]. Febrile infection-related epilepsy syndrome (FIRES) is a subcategory of NORSE, applicable to all ages, that requires a febrile infection starting between 2 weeks and 24 h prior to the onset of refractory status epilepticus [1]. Regarding the etiology, a viral infection has been hypothesized due to the evidence of lymphocytic pleocytosis in the cerebrospinal fluid (CSF). Another possible hypothesis is an autoimmune etiology supported by the good response to immunomodulatory therapies (steroids, immunoglobulins, plasma exchange). Brain MRI is usually unrevealing or it can show non-specific alterations related to the continuous epileptic activity. Here, we report a peculiar neuroradiological picture associated with FIRES in an adult patient.

Case report

A 29-year-old man presented a generalized tonic-clonic seizure (GTCS) 1 week after a febrile episode. His personal and family histories were unremarkable for any neurological disease. He was referred to the emergency department where he presented another GTCS followed by psychomotor agitation. A brain CT scan was negative and antibiotic and antiviral therapy associated with sedatives were started, considering the hypothesis of a central nervous system infection. He continued to present agitation and seizures characterized by ocular deviation and clonic movements of the hemi-face and arms, with inconstant lateralization and, sometimes, with bilateral diffusion and no recovery of awareness between seizures. He was then referred to the intensive care unit (ICU) where he was treated with deep sedation using propofol (4 mg/kg/h) and a combination of high doses of antiepileptic drugs (phenobarbital at a maximum dosage of 400 mg/day, levetiracetam at 2000 mg/day, and lacosamide at 400 mg/day). For the lack of any clinical response, a cycle of immunoglobulins (0.4 g/kg/day for 5 days) was then administered.

The electroencephalographic recordings showed slowing of the background activity and subcontinuous delta waves, with high voltage spikes over the frontal-temporal regions with inconstant right prevalence. The attempt of reducing the deep sedation, during EEG monitoring, led to the reappearance of continuous ictal discharges over the temporal regions, asynchronous over the two hemispheres, with frequent and rapid bilateral spreading. After 22 days from the onset, he presented a clinical and EEG improvement that allowed to reduce the sedation.

Several CSF examinations were performed but none of these was remarkable, except for a slight increase in proteins (66.4 mg/dl; normal values 20–35 mg/dl). Extensive and repeated researches for infectious agents and auto-antibodies (including anti-VGKC-complex, anti-NMDAR, anti-AMPAR, anti-GABAbR) on serum and on CSF were performed and all of them were negative. Therefore, a diagnosis of FIRES was hypothesized.

Serial brain MRI performed in our patient revealed atypical findings with a peculiar temporal course. The first MRI performed 24 h after the onset showed a

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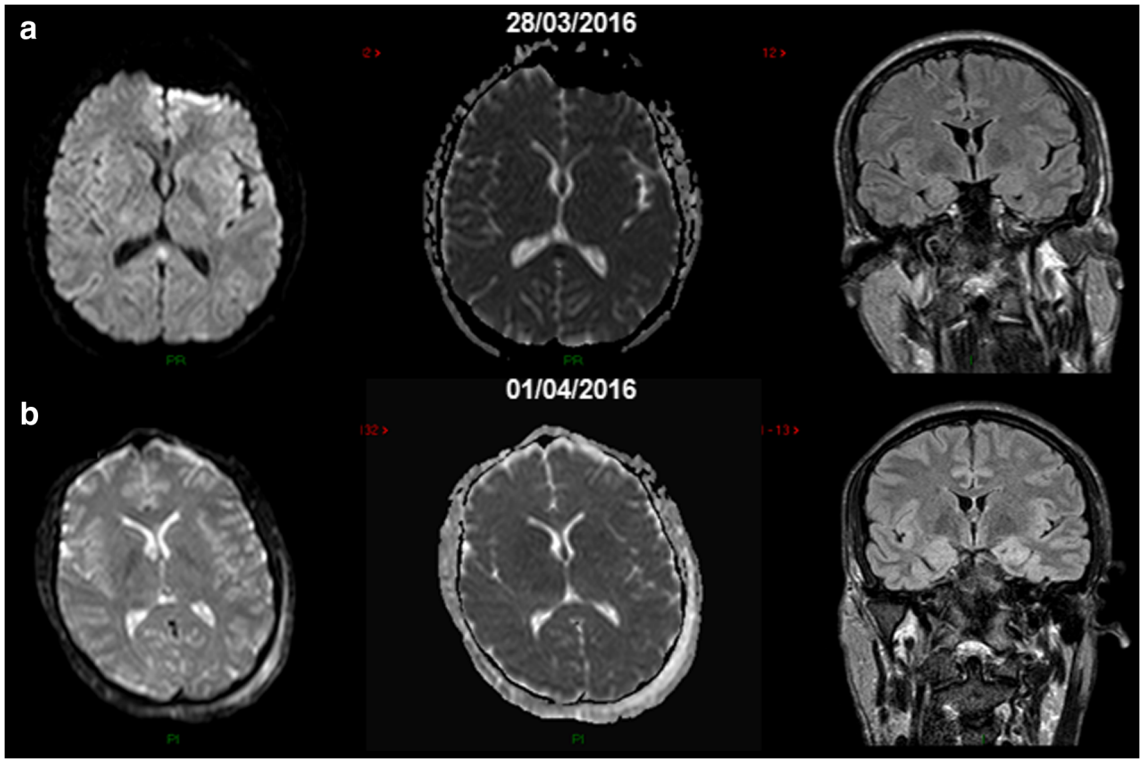

Fig. 1 **a** Brain MRI performed 24 h after the onset of the status showing, in the splenium of the corpus callosum, a hyperintense signal on DWI series, with restriction in ADC images, without hippocampal alterations (in FLAIR sequences). **b** Brain MRI performed 4 days after the onset showing disappearance of the splenial lesion, with slight hyperintensity of the hippocampi in FLAIR images

small, oval-shaped high-intensity signal on T2- and diffusion-weighted series with restriction in ADC series in the splenium of the corpus callosum, without gadolinium enhancement (Fig. 1a). Four days later, a second MRI showed a slight hyperintense signal in T2-weighted and FLAIR series over both hippocampi with the disappearance of the corpus callosum lesion (Fig. 1b). Twenty days after the resolution of the status, a new MRI showed only an increase of the bilateral hippocampal hyperintensities (Fig. 2).

At 2 years follow up, the patient still presents memory and attention deficits and weekly focal motor seizures. The bilateral hyperintense signal of the hippocampal regions is still present, though reduced compared with the previous findings.

Discussion

Reversible splenial lesion is a specific sign usually found in mild encephalitis/encephalopathy with a reversible splenial lesion (MERS), a form of encephalopathy characterized by altered consciousness, ataxia, and seizures [2]. Its main characteristic is the benign course with complete recovery, both clinically and radiologically, in few weeks. A reversible splenial lesion can occasionally be found in patients undergoing withdrawal of antiepileptic drugs, usually for disorders other than epilepsy but it has also been reported in a 2-year-old child with status epilepticus [3]. The pathogenesis of this alteration is not clear but it seems to be secondary to transient interstitial edema, occurring in this region due to its higher vulnerability to excitotoxic injury [2]. In our case, the persistence of refractory status epilepticus led us to the exclusion of the diagnosis of MERS. During the status and after its resolution, bilateral hippocampal hyperintensities were found. This radiological feature has been also described in autoimmune encephalites, specifically limbic encephalitis, a disease characterized by subacute onset of working memory deficits, psychiatric symptoms or seizures, EEG and radiological bilateral temporal involvement, and CSF pleocytosis. However, our patient presented exclusively seizures with an abrupt onset, thus not fulfilling the diagnostic criteria for definite autoimmune limbic encephalitis [4]. Moreover, the search for the most common causes of limbic encephalitis gave negative results.

Many authors reported MRI changes after status epilepticus, the most frequent being the alterations in the hippocampi, with possible extension to ipsilateral thalamus and contralateral cerebellum, functionally connected areas [5], but also in other areas, such as splenium of

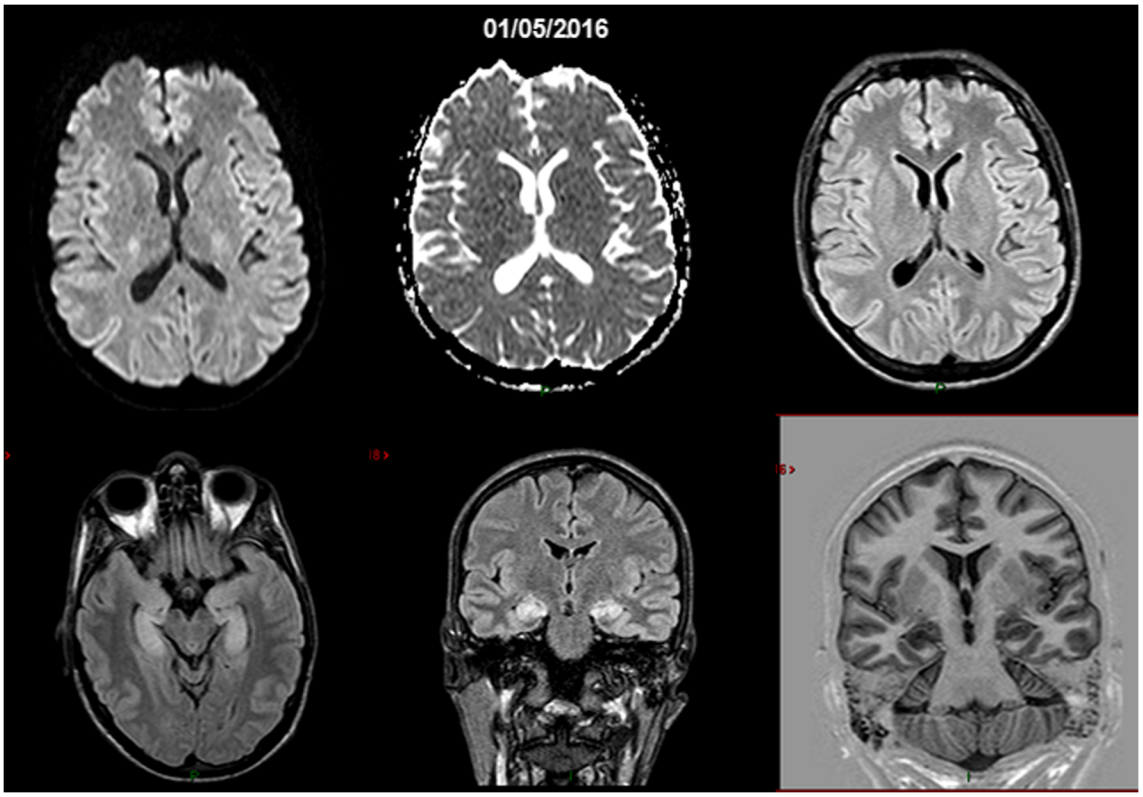

Fig. 2 Brain MRI performed after the resolution of the status showing increased hyperintense signals of bilateral hippocampi

the corpus callosum, basal ganglia, and subcortical white matter [3]. The hippocampal alterations may be due to cytotoxic edema, hyperfusion, and altered blood-brain barrier. However, reliable scientific data about the pathogenesis of these alterations and their appearance after persistent ictal activity are still missing. The temporal evolution of the hippocampal modifications in our patient seems to reveal that they could be the consequences of the epileptogenesis rather than the causes. Alterations in both hippocampi and in other cortical regions (cingulate gyrus, claustrum, and temporal, parietal, frontal, and occipital lobes) have already been described in patients affected by FIRES and NORSE [5]. Furthermore, the presence of a reversible splenial lesion in one case of FIRES in a 7-year-old child has been reported as an early neuroradiological finding [6]. Recently, communication fibers between the two medial temporal lobes have been found in the splenium of the corpus callosum using advanced tractography methods [7], thus possibly explaining the involvement of this region during persistent temporal ictal activity.

To our knowledge, this is the first case of FIRES in an adult patient with such MRI findings. The neuroradiological description of our patient, together with the previously described case, can be useful for an early diagnosis of this rare clinical condition and may offer new insights about the physiopathology of the disease.

Compliance with ethical standards The patient's consent was obtained for publication of this case report.

Conflict of interest The authors declare that they have no conflict of interest.

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