



# A case of febrile infection-related epilepsy syndrome (FIRES) in young adult: still a diagnostic and therapeutic challenge

Roberto Acampora<sup>1</sup> · Pablo Quiroga Subirana<sup>2</sup> · Luana Durante<sup>1</sup> · Rossella Tonziello<sup>3</sup> · Giuseppina Aversano<sup>4</sup> · Maria Lieto<sup>1</sup> · Patrizia Ripa<sup>1</sup> · Maria Pia Mazzaferro<sup>1</sup>

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## Abstract

A new onset of status epilepticus in a previously healthy adult preceded by a recent minor febrile infection represents a diagnostic and therapeutic challenge in clinical practice. Considering the broad spectrum of epileptic encephalopathies caused by autoimmune mechanisms, differential diagnosis for new-onset refractory status epilepticus (NORSE) should include febrile infection-related epilepsy syndrome (FIRES), in order to not underestimate the underlying etiological condition triggering epilepsy in non-epileptic patients (Hon et al. in *Recent Pat Inflamm Allergy Drug Discov* 12:128–135, 2018). We report a case of acute encephalopathy with refractory seizures after a febrile illness (FIRES) in a young adult with complete remission of symptoms as well as dramatic improvement of EEG abnormalities following intravenous immunoglobulin and proper antiepileptic medications. We conducted an extensive workup including lumbar puncture, blood tests, EEG serial monitoring, MRI brain, total body CT scan, and PET brain with FDG to shed light on the etiology of the disease.

**Keywords** NORSE · FIRES · Immunoglobulin · Antiepileptic drugs (AED) · Epilepsy

## Case report

A 23-year-old male, without any mention of relevant disease in his past medical history or family history attended the emergency room of our hospital for an episode of generalized seizure. In the 2 weeks prior to admission, during a trip in Turkey, the patient had experienced a flulike illness with fever, myalgia, and asthenia without any sequelae; in that occasion, a SARS-CoV2 infection was ruled out. However, during the hospitalization, he underwent a brain MRI (1.5-T), performed 3 days after the convulsive generalized seizure, which showed a focal hyperintensity on the left insula region, whereas serial EEG showed occasional sharp waves

in both temporal regions. Due to the fact that patient, after a week of observation in our department, did not present any other seizures, he was discharged with levetiracetam 1000 mg a day.

On the day after, he attended again our ER suffering from a generalized convulsive status epilepticus (SE) which did not respond to the first and second line antiseizure medications such as diazepam, levetiracetam, valproic acid, and lacosamide. Hence, he was treated with midazolam (5 mg e.v) with immediate cessation of the SE. Therefore, the patient was again hospitalized and underwent a lumbar puncture which was unrevealing: CSF analysis indeed showed no cells and normal glucose and protein levels. No immunoreactivity was detected to intracytoplasmic neural antigens (Hu, Ri, Yo, Ma2, Amphiphysin, CV2,) or to surface antigens (NMDAR, VGKC complex, AMPA-R, GABAB-R, Gly-R). Serological and PCR tests for neurotropic viruses (including herpes group viruses and HIV) were negative. A brain MRI performed 5 days after status epilepticus onset showed marked hyperintense area in both insular regions (Fig. 1). These MRI findings were suggestive of an inflammatory process involving cortical areas (*claustrum sign*) although they have also been described in literature as a consequence of repeated seizures [2]. EEG

✉ Roberto Acampora  
roberto.acampora3@virgilio.it

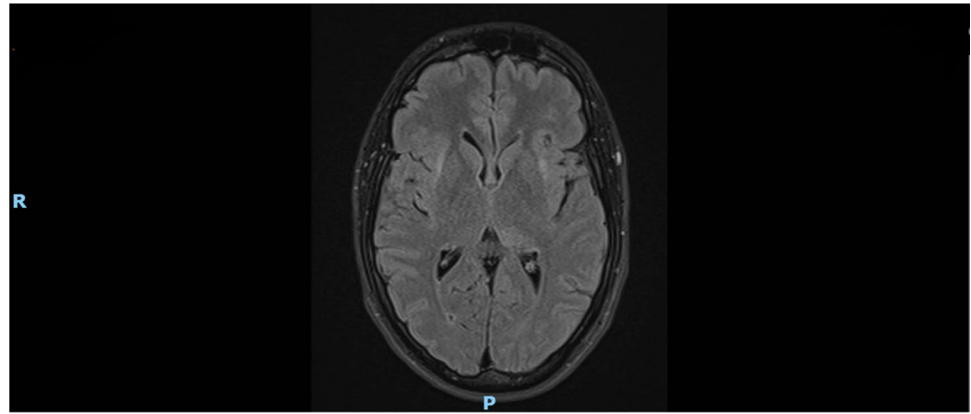
<sup>1</sup> Neurology-Stroke Unit, Ospedale del Mare Hospital, Naples, Italy

<sup>2</sup> Neurology-University Hospital of Torrecardenas, Almeria, Spain

<sup>3</sup> Medicine-Rizzoli Hospital, Ischia, Italy

<sup>4</sup> Faculty of Medicine, University of Naples “L. Vanvitelli”, Naples, Italy

**Fig. 1** Brain MRI. FLAIR sequences showing hyperintense areas in both insular/claustrium regions (claustrium sign)

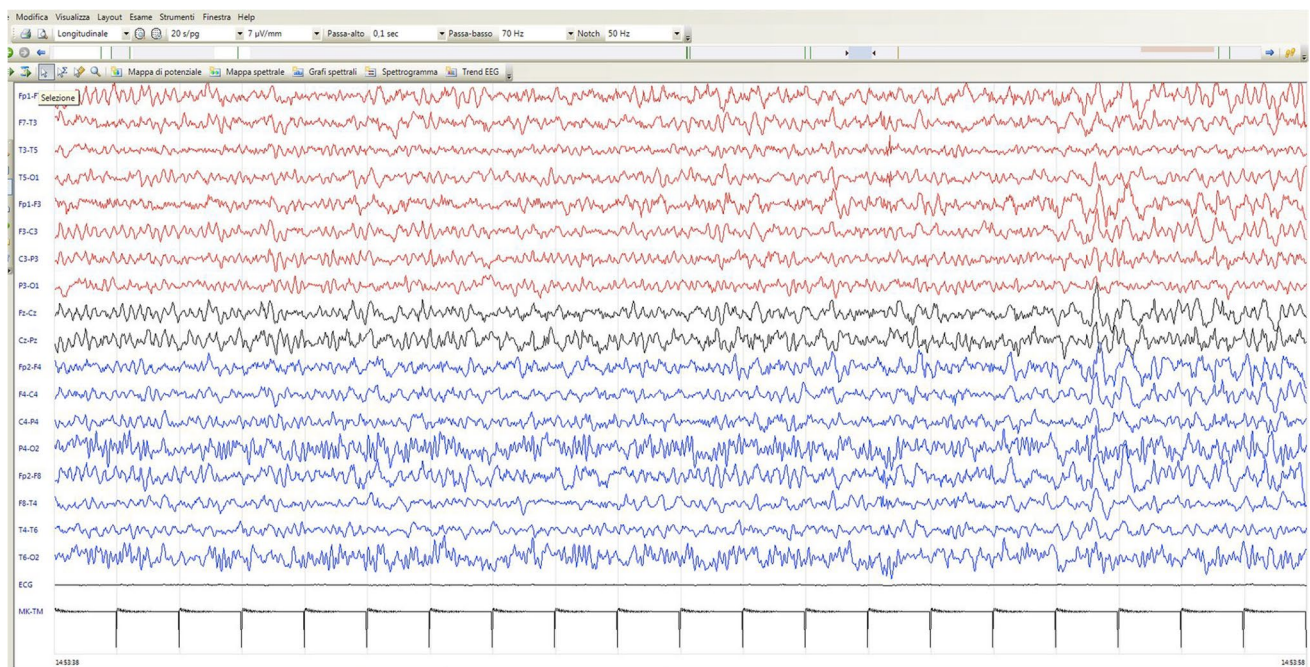


monitoring showed abundant irritative activity composed of well-formed sharp waves and slow waves in the frontal and temporal regions bilaterally (Fig. 2).

Furthermore, on completion of investigation, a total-body CT scan performed for the pursuit of occult neoplasms was negative, whereas a PET FDG brain resulted inconclusive.

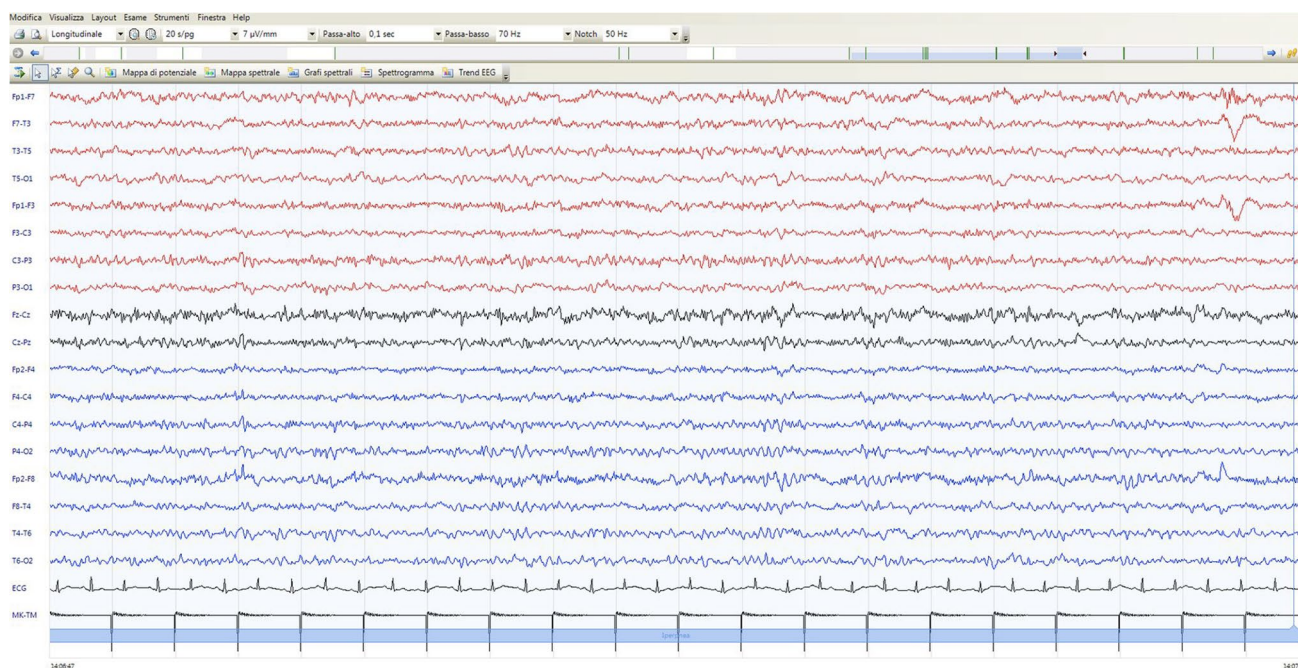
Accordingly to the above findings, due to the persistence of abundant epileptiform activity on EEG monitoring despite he had received several antiseizure medications as levetiracetam (2000 mg/day), valproic acid (1200 mg/day), perampanel (6 mg/day), and lacosamide (400 mg/day) during hospitalization, a diagnosis of FIRES was

hypothesized. As a consequence, the patient underwent an empiric immunomodulation treatment based first on high doses of steroids (1 g per day of methylprednisolone for 5 consecutive days) without any improvement, followed by immunoglobulin, i.e. (1 g/kg/day for 5 days) with a dramatic improvement both from the clinical and electroencephalographic standpoint (Fig. 3). One month after onset, the patient was asymptomatic and received brivaracetam, lacosamide, and clonazepam as secondary monotherapy. After 12 months follow-up, the patient had no longer seizures and EEG, and brain MRI repeated within this timeframe was normal.



**Fig. 2** EEG standard performed the day after SE (status epilepticus) showing abundant epileptic activity mainly characterized by sharp waves and slow waves in the frontal and temporal regions bilaterally.

During the recording of the EEG, the patient was on valproic acid (1200 mg/day), lacosamide (400 mg/day)



**Fig. 3** EEG standard performed after immunomodulation treatment (at the end of hospitalization period) no revealing epileptic activity

## Discussion

We recently diagnosed a patient with a FIRES syndrome, considered a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 h prior to onset of refractory status epilepticus, with or without fever at onset of status epilepticus [3]. Such condition is very rare, including approximately 200 FIRES cases described worldwide with an estimated incidence of 3.4–7.2 per 100,000 per year [4, 5]. It has been hypothesized that FIRES is caused by a disimmune mechanism involving a cross-reaction of the immune system during an infection resembling an encephalitis autoimmune causing a new onset refractory status epilepticus (NORSE). To date, data published in literature showed that almost all patients with NORSE had suffered from an infection as non-specific influenza-like illness with headache, gastrointestinal, or upper respiratory infections within 2 weeks prior to the onset of symptoms. Respiratory tract infections were the most common (more than 50%). The presence of fever is mandatory for the diagnosis of FIRES and precedes the illness in up to 60% of adults.

Up to 50% of patients with FIRES may have an underlying autoimmune encephalitis (anti-NMDA and anti-VGKC: including anti-LG1 or anti-CASPR2) or viral CNS infections, genetic and metabolic/toxic encephalopathy. Among the putative causes autoimmune encephalitis, sporadic or paraneoplastic, is the most common cause identified in adult with FIRES [6]. Our patient was asymptomatic after

the acute phase and after one year of follow-up. However, majority of patients, especially children, did not obtain positive outcomes despite the use of immunomodulatory therapy (i.e. methylprednisolone pulses or intravenous immunoglobulin). Nevertheless, as described in literature is likely the existence of a benign subgroup of patients with FIRES, especially adults, which better respond to the first or second line immunosuppressive therapy determining a good clinical outcome [7].

In conclusion, by presenting this case, we want to raise awareness on the importance of timely recognizing FIRES syndrome when face with young adults with a presentation of frequent seizures or status epilepticus, especially in patients without no story of epilepsy in the past medical history, taking into account that the prognosis of FIRES may be better in adults. Indeed, although to date, no specific therapy exists for FIRES and NORSE, we recommend an extensive workup aimed to avoid misdiagnosis of the illness and timely treat the patient in order to reduce clinical sequelae.

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