Seizure 22 (2013) 153–155

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Case report

The expanding spectrum of febrile infection-related epilepsy syndrome (FIRES)

Pedro J. Serrano-Castro *, Pablo Quiroga-Subirana, Manuel Payán-Ortiz, Javier Fernandez-Perez

Neurology and Neurophysiology Unit, Complejo Hospitalario Torrecárdenas, Almeria, Spain

ARTICLE INFO

Article history:
Received 23 October 2012
Received in revised form 15 November 2012
Accepted 16 November 2012

Keywords:
Febrile infection-related epilepsy syndrome
Inmunology
Epilepsy
Encephalopathy

1. Introduction

In recent years, a number of phenomena included in the group of probable epileptic encephalopathies of autoimmune origin have been described. Their common denominator is abrupt onset, usually after a self-limited febrile illness, and a clinical picture of repetitive seizures or difficult-to-control status epilepticus. These symptoms occur mostly in children and have received a wide range of names, despite their highly similar presentations with minor distinctive aspects. Such denominations include acute encephalitis with refractory repetitive partial seizures (AERRPS),[1] febrile infection-related epilepsy syndrome (FIRES)[2] or new-onset refractory status epilepticus (NORSE).[3]

Recently, several authors have advocated a simplification of this heterogeneous range of diagnoses, with Ismail and Kossoff[4] suggesting the definition of a single post-infectious syndrome with common characteristics.

We report a case of acute encephalopathy after a febrile illness with complete remission of symptoms following antiepileptic and steroid treatment. We conducted an extensive workup including Video-EEG monitoring and speculate on the nature and classification of these syndromes and their growing clinical spectrum.

2. Case report

The patient was a 19-year-old female with no relevant personal or family history. She was born after normal pregnancy and delivery and she also had normal acquisition of psychomotor developmental milestones. There were no significant comorbid conditions.

In the week prior to admission, the patient experienced a flu-like illness with fever, myalgia and malaise. Within a week, she developed sudden-onset paroxysmal episodes of a painful "cramping" affecting the right arm and hand, and occasionally the right leg, with Jacksonian progression to the face, dysarthria, salivation, and clustering (up to 30–40 episodes in 1 day). She remained conscious throughout the episodes and could remember them. This situation was also present 3 days prior to admission.

Brain MRI performed 3 days after seizure onset showed a hyperintense area in both insular regions, more evident on the right (Fig. 1). These MRI findings are suggestive of an inflammatory process involving cortical areas although they have also been described as a consequence of repeated seizures.[5]

Video-EEG monitoring showed abundant seizure episodes similar to those described by the patient, even during sleep. The nocturnal episodes coincided with irritative activity composed of spikes and sharp waves starting in the temporal regions bilaterally and reflected clinically as versive head deviation, as well as oral

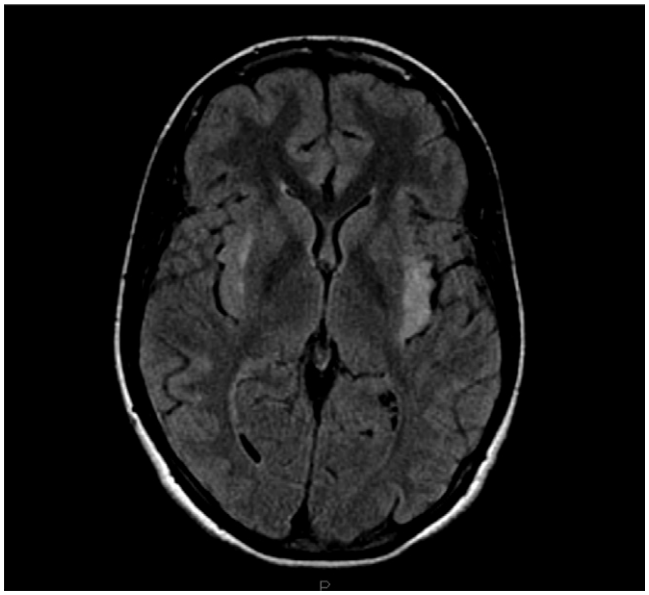

Fig. 1. MR imaging in acute phase. Axial FLAIR sequences. Hyperintense area in both insular regions, more evident on the right.

* Corresponding author. Tel.: +34 671562365; fax: +34 950016284.
E-mail address: pedro.serrano.c@gmail.com (P.J. Serrano-Castro).

http://dx.doi.org/10.1016/j.seizure.2012.11.006

Table 1
Revision of the previous series of FIRES concerning to the outcome and immunosuppressive treatments. IvIg, intravenous immunoglobulin; y-o, years old; and MP, methylprednisolone pulses. Patient of series by van Baalen are included in the series by Kramer.

	Patients with normal intellectual outcome (%)	Median age (range) in normal outcome patients vs cognitive impairment patients or death	Immunosuppressive treatment (IS) in normal outcome patients		IS in the patients with cognitive impairment patients or death	
[10]	12/77 (15.58%)	9.3 y-o (range 2–15) vs 7.6 y-o (range 2–17)	No treatment 5/12 (41.6%) IS treatment, 7/12 (58.4%)	IvIg 1/12 (8.3%) MP 2/12 (16.6%) MP + IgIV 4/12 (33.2%)	No treatment 8/65 (12.3%) IS treatment 26/65 (40%) Unknown 31/65 (47.7%)	IvIG 11/65 (16.9%) MP 4/65 (6.1%) MP + IvIg 11/65 (16.9%)
[2]	2/22 (9.09%)	10 y-o (range 9–11) vs 7.5 y-o (range 3–15)	No treatment 2/2 (100%)		No treatment 10/20 (50%) IS treatment 10/20 (50%)	

and swallowing automatisms (Supplementary Video 1). There was no secondary generalization.

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2012.11.006.

CSF analysis showed 6 cells and normal glucose and protein levels. No immunoreactivity was detected to intracytoplasmic neural antigens (Hu, Ri, Yo, Amphiphysin) or to surface antigens (NMDAR, LGI1 or other potassium channels). Serological and PCR tests for neurotropic viruses (including herpes group viruses and HIV) were negative.

A neuroimaging screen for occult neoplasms, including a specific search for ovarian teratomas, was also negative.

IV levetiracetam, clonazepam and methylprednisolone pulses (1000 mg/day for 5 consecutive days) were administered. There was dramatic improvement both from the clinical and neuroimaging standpoint. One month after onset, the patient was asymptomatic and receiving eslicarbazepine acetate as secondary monotherapy.

3. Discussion

The clinical spectrum of epileptic encephalopathies of autoimmune origin has expanded greatly in the last 30 years.[6]

Traditionally, limbic encephalitis was the prototype of these diseases, which were typically conceived as paraneoplastic syndromes associated with antibodies directed against intracellular targets (onconeural antigens) and usually had a poor outcome despite immunomodulatory therapy.[7]

The following years saw the description of a number of antibodies directed against extracellular targets (known as surface antigens) representing neural protein domains in their native conformation,[8] especially those directed against voltage-gated potassium channels (VGKC) and, more recently, those directed against receptors of the N-methyl-D-aspartate (NMDA) complex.[9] The common denominator of these manifestations was the presence of limbic encephalitis, clinically defined by the triad of amnesia, disorientation and complex partial seizures. Over the last two years, the subgroup of patients with limbic encephalitis associated with VGKC antibodies has been subdivided by virtue of our ability to identify specific ligands within the receptor. Thus, we have identified syndromes associated with the presence of antibodies against the leucine-rich, glioma-inactivated protein (LGI1) (related to limbic encephalitis with acute dystonic faciobrachial seizures) and with contactin-associated protein 2 (CASPR2) or contactin-2, which are more related to peripheral nervous system impairment of the neuromyotonia or Morvan syndrome type.

In recent years, another subtype of syndromes has been defined, also presumed to be autoimmune in nature, but with two common features: febrile infection in the weeks prior to the acute onset of an extraordinary high seizure activity most difficult to treat.

These include the so-called febrile infection-related epilepsy syndrome (FIRES). van Baalen et al.[2] and Kramer et al.[10] published the most important series describing this phenomenon to date and outlined the clinical profile of FIRES. Symptoms were most prevalent in patients under the age of 15, and there was a slight male predominance. All patients had suffered an infection in the week prior to the onset of symptoms. Respiratory tract infections were the most common (more than 50%). The natural history of FIRES is typically biphasic, with a seizure-free period between the resolution of fever and the onset of symptoms ranging from 2 to 14 days. Thereafter, the acute period of the disease develops, lasting from 1 to 12 weeks (mean, 3 weeks). Most cases had a poor prognosis; the mortality rate was 9% and many patients were left with cognitive sequelae, which were occasionally severe.

Apart from antibody-related encephalitis, other pathogenetic mechanisms have been proposed for FIRES. These alternative hypotheses grant a special role to the innate immune system[11] or even to a genetic predisposition.[12]

Our case meets the diagnostic criteria for FIRES, with several characteristics that seem relevant.

The first concerns its localization in terms of the epileptogenic region. In most cases of FIRES described hitherto, the epileptogenic zone identified is limited to the medial temporal lobe. In our case, however, acute phase MRI studies identify hyperintensities located in bilateral insular areas without evidence of hippocampal damage. Four cases previously reported by van Baalen and Kramer[2,10] also showed unilateral or bilateral insular involvement. We clarify that patients with insular involvement in both series are the same. Any case, insular damage must be considered a rare location in FIRES as it has been described in less than 9% of cases reported in the most relevant series.

The second difference concerns prognosis. Our patient was asymptomatic after the acute phase and after one year of follow-up. Most patients in previous series did not obtain positive outcomes despite the use of immunomodulatory therapy (i.e. methylprednisolone pulses or intravenous immunoglobulin).

Nevertheless, around 15% of the patients had a good medium-term evolution despite the fact that FIRES is considered a "catastrophic syndrome" (Table 1). In addition, 7 out of 14 patients who showed good evolution had not received any type of immunosuppressive therapy. Moreover, our case suggests the existence of a benign subgroup of patients with FIRES. Table 1 shows that these patients tend to be older than those with worse evolution (9.4 years old vs. 7.5 years old). This may be explained by the fact that an older brain is also a fully mature brain. Our patient was 19 years old and, therefore, probably had more possibilities of obtaining a good outcome.

Our case serves as a warning sign of the increasing recognition of febrile infection-related epileptic encephalopathies that are not necessarily confined to children or localized to the medial temporal lobe. The prognosis of FIRES may be better in adults.

References

1. Sakuma H, Awaya Y, Shiomi M, Yamanouchi H, Takahashi Y, Saito Y, et al. Acute encephalitis with refractory, repetitive partial seizures (AERRPS): a peculiar form of childhood encephalitis. *Acta Neurologica Scandinavica* 2010;**121**(4): 251–6.
2. van Baalen A, Häusler M, Boor R, Rohr A, Sperner J, Kurlemann G, et al. Febrile infection-related epilepsy syndrome (FIRES): a nonencephalitic encephalopathy in childhood. *Epilepsia* 2010;**51**(7):1323–8.
3. Wilder-Smith EP, Lim EC, Teoh HL, Sharma VK, Tan JJ, Chan BP, et al. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. *Annals of the Academy of Medicine Singapore* 2005;**34**(7): 417–20.
4. Ismail FY, Kossoff EH. AERRPS, DESC, NORSE, FIRES: multi-labeling or distinct epileptic entities? *Epilepsia* 2011;**52**(11):e185–9.
5. Huang YC, Weng HH, Tsai YT, Huang YC, Hsiao MC, Wu CY, et al. Periictal magnetic resonance imaging in status epilepticus. *Epilepsy Research* 2009;**86**(1):72–81.
6. Irani SR, Vincent A. The expanding spectrum of clinically distinctive, immunotherapy-responsive autoimmune encephalopathies. *Arquivos de Neuro-Psiquiatria* 2012;**70**(April (4)):300–4.
7. Vincent A, Lily O, Palace J. Pathogenic autoantibodies to neuronal proteins in neurological disorders. *Journal of Neuroimmunology* 1999;**100**(1–2):169–80.
8. Irani SR, Bien CG, Lang B. Autoimmune epilepsies. *Current Opinion in Neurology* 2011;**24**(2):146–53.
9. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA receptor encephalitis: case series and analysis of the effects ofantibodies. *The Lancet Neurology* 2008;**7**(12):1091–8.
10. Kramer U, Chi CS, Lin KL, Specchio N, Sahin M, Olson H, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. *Epilepsia* 2011;**52**(11):1956–65.
11. Nabbout R, Vezzani A, Dulac O, Chiron C. Acute encephalopathy with inflammation-mediated status epilepticus. *The Lancet Neurology* 2011;**10**(1):99–108.
12. Howell KB, Katanyuwong K, Mackay MT, Bailey CA, Scheffer IE, Freeman JL, et al. Long-term follow-up of febrile infection-related epilepsy syndrome. *Epilepsia* 2012;**53**(1):101–10.