

Status epilepticus in a patient with fragile X syndrome: electro-clinical features and peri-ictal neuroimaging

Carlo Di Bonaventura¹, Francesco Mari^{1,2}, Alberto Pierallini^{1,3}, Oriano Mecarelli¹, Franco Randi¹, Mario Manfredi^{1,2}, Massimiliano Prencipe¹, Anna Teresa Giallonardo^{1,2}

¹ Department of Neurological Sciences

² Neuromed Institute of Pozzilli (IS), University of Rome "La Sapienza"

³ San Raffaele IRCCS, Rome, Italy

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ABSTRACT – Fragile X syndrome (Fra-X) is a common cause of mental retardation that can be associated with partial epilepsy characterized by a variety of electro-clinical features. A wide spectrum of interictal activities are reported, although no data regarding ictal EEG activity have as yet been published. Drug-resistant seizures are uncommon, and the occurrence of clustering seizures or status epilepticus has only been reported anecdotally. We describe a Fra-X patient with refractory partial epilepsy related to a malformation of cortical development who experienced a partial status epilepticus that was well documented by video-EEG and MRI. We report the electro-clinical features and peri-ictal neuroimaging data.

Key words: fragile X syndrome, status epilepticus, partial epilepsy, peri-ictal neuroimaging, cortical dysplasia

Fragile X syndrome (Fra-X) is the second most common cause of identifiable, genetic mental disability after Down's syndrome. It was originally described as a cytogenetic abnormality located in the long arm the X chromosome. The responsible FMR1 gene at Xq27.3 was the first gene to be shown with a trinucleotide repeat sequence (CGG) subject to amplification (Yu *et al.* 1991). In fact, nearly all mutations (> 99%) in the FMR1 gene resulting in fragile X syndrome occur as trinucleotide repeat (CGG) expansion accompanied by aberrant methylation of the gene. Deletions and point mutations in FMR1 account for the remaining mutations found in indivi-

duals with the syndrome. Methylation of the CGG expansion results in decreased or completely absent FMR1 transcription and the loss of the encoded protein (FMRP). FMRP is a nucleocytoplasmic shuttling protein that binds several mRNAs, including its own mRNA; it forms messenger ribonucleoprotein complexes, and associates with translating ribosomes (Ceman *et al.* 1999). It is most abundant in neurons and appears to play a role in structural and functional maturation of synapses (Weiler and Greenough 1999).

The phenotype of this disorder includes moderate to severe mental retardation, characteristic appearance

Correspondence:

C. Di Bonaventura,
Viale dell'Università 30,
00185 Rome,
Italy
<c_dibonaventura@yahoo.it>

(large head, long face, prominent forehead and chin, protruding ears), connective tissue findings (joint laxity), and macro-orchidism (postpubertally). Behavioral abnormalities, sometimes including autism spectrum disorder, are common. The occurrence of epileptic seizures in the Fra-X population is currently estimated about 14-18% (Musumeci *et al.* 1999). Several groups of Fra-X patients have been described on the basis of their electro-clinical patterns, the least frequent being the rare group with severe, drug-resistant epilepsy. In this last group, the occurrence of clustering seizures constituting a partial status epilepticus has been anecdotally reported without electro-clinical documentation (Incorpora *et al.* 2002). We describe a Fra-X patient with drug-resistant partial epilepsy related to a malformation of cortical development and a well-documented video-EEG partial status epilepticus; a complete peri-ictal neuroimaging study was also performed.

Case study

A 15-year-old male patient with Fra-X affected by drug-resistant partial epilepsy. Pregnancy and delivery were referred as normal, although mild, delayed psychomotor development (inability to stand and explore the environment, difficult relationship with maternal and external stimuli) was noted from the first year of life. A presumptive diagnosis of Fra-X was made at the age of six following cytogenetic analysis. This diagnosis was successively confirmed by molecular genetic testing and his mother was found to be an Fra-X carrier. Besides mild mental retardation, clinical features included the characteristic facial dysmorphism (large ears, prominent jaw) and macro-orchidism.

Seizures first occurred at the age of 5 years, with partial motor seizures consisting of eye and head deviation to the right, sometimes followed by secondary generalization. Seizures, which usually occurred as prolonged clusters, were consistently drug-resistant. Before coming to our attention, the patient's therapy had, for the previous two years, consisted of Acetazolamide 750 mg/d and Clobazam 40 mg/d, but seizures had persisted at a weekly frequency.

The patient had recently been referred to an emergency department because of a high fever associated with abdominal pain and vomiting, but clinical and laboratory tests had not revealed any disease; the patient was admitted for further investigations, with a presumptive diagnosis of viral gastroenteritis; any acute pathology involving the CNS was excluded. However, while hospitalised, the patient was, following an extremely prolonged cluster of seizures, referred to our clinic for a neurological evaluation and specific therapy. He underwent video-EEG monitoring, which documented recurrent and prolonged partial seizures constituting a status epilepticus (SE).

Clinically, the seizures were characterized by initial motor signs consisting of slow eye opening and eye and head tonic deviation to the right associated with facial flushing, midriasis, lacrimation and lateralized clonic movements involving the right oral muscles; late signs consisted of fast clonic, nystagmus-like eye movements to the right. The clinical mean duration of each ictal event was about 3 minutes, with full consciousness not being regained in the post-ictal phase. Video-EEG showed a complex, monomorphic pattern consisting of ictal activity arising in the left posterior temporal regions with extensive spreading, followed by an apparently independent recruiting activity in the anterior regions on the same side (figure 1). This independent recruiting activity usually persisted for some minutes, but was not accompanied by any clinical signs. The SE was refractory to a first line therapeutic approach with i.v. benzodiazepines (lorazepam 8 mg as a bolus, followed by a maintenance dose of 16 mg/24h) and phenytoin (750 mg as a bolus, followed by 500 mg/24h). Since the seizures persisted and consciousness was constantly impaired, after 48 hours the patient was given anaesthesiological assistance (including artificial ventilatory support), as well as therapy consisting of a combination of phenytoin (maintenance dose of 15 mg/Kg), thiopentale (250 mg as a bolus, followed by continuous infusion of 5 mg/Kg/h). After almost 60 hours, this therapy led to the SE resolving, and the disappearance of both seizures and ictal activity on the EEG.

After thiopentale administration was discontinued, consciousness was gradually regained and the outcome proved excellent. After i.v. drug discontinuation, *per os* therapy with phenytoin 300 mg per day and phenobarbital 100 mg per day achieved complete seizure control. In a neuroradiological evaluation performed few months before the SE, the MRI had showed a cortical development malformation located in the left temporal lobe and characterized by a T1-weighted slight thickening and T2 FLAIR hyperintensity of the hippocampal cortex (figure 2A); hypodevelopment of the left hemisphere, asymmetry of the supratentorial ventricular system (STVS) (enlargement of the right lateral ventricle) and a supravermian arachnoid cyst were also evident (figure 2B). During the SE, conventional and diffusion-weighted MRI (DWI), showed a wide, left hemispheric signal alteration involving the fronto-temporo-parietal regions (figure 2C). After resolution of the SE, 60- and 90-day MRI follow-up examinations showed complete resolution of the left hemispheric signal alteration.

Discussion

This case is highly interesting from both an electro-clinical and a neuroimaging point of view. It is the first reported case of a well-documented video-EEG partial SE in a patient with Fra-X. To our knowledge, SE has previously

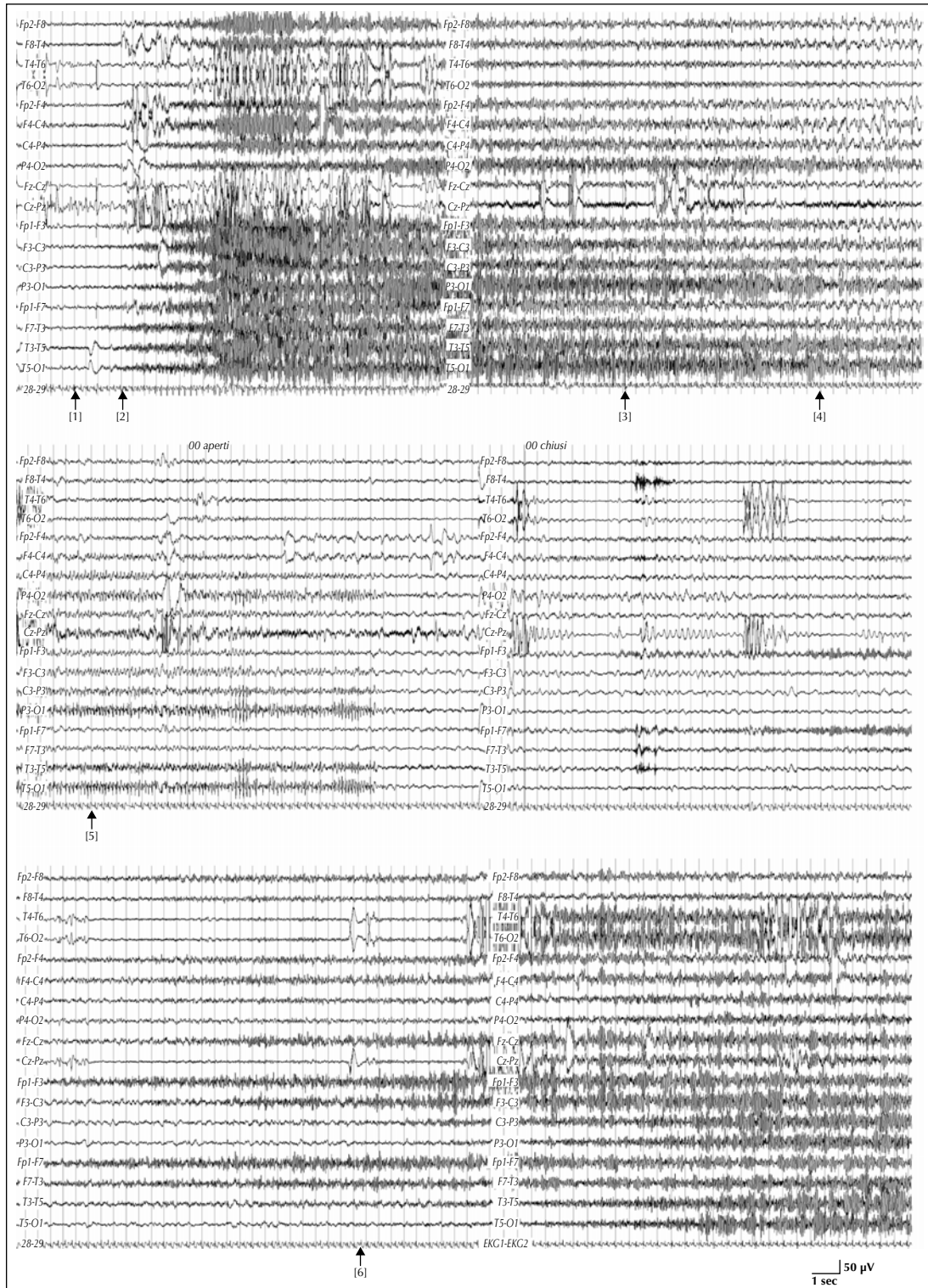


Figure 1. EEG pattern and electro-clinical correlation of video-EEG-documented recurrent seizures. Ictal recruiting fast activity arising from the left posterior temporal regions with extensive spreading, followed by a persisting polyspike-and-wave discharge in the left posterior regions and renewed recruiting activity in the left frontal areas. [1] = slow eye opening, [2] = eye and head deviation to the right, [3] = eye clonic nystagmus-like movements to the right, [4] = clonic movements involving the right facial muscles, [5] = end of lateralized clonic movements, [6] = eye opening.

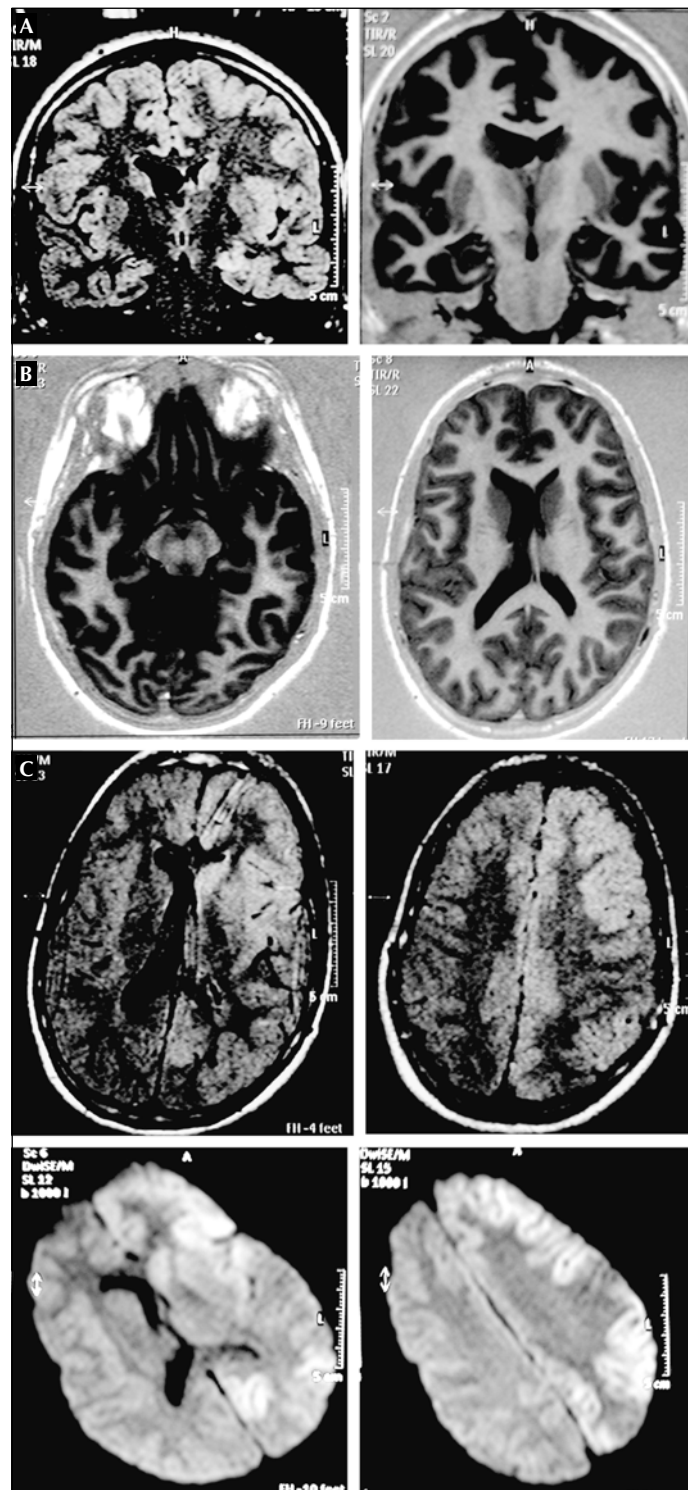


Figure 2. MRI images. **A)** Coronal T2-weighted FLAIR images show a hyperintensity in left hippocampal region; at the same level T1-weighted IR images show a slight thickening of the corresponding cortex. **B)** Hypodevelopment of left hemisphere, asymmetry of supratentorial ventricular system (enlargement of right lateral ventricle) and a supraventricular arachnoid cyst are also evident. **C)** MRI images obtained during status epilepticus after 2 days of sustained ictal activity; T2-weighted FLAIR and diffusion weighted images show slight hyperintensity in the left fronto-temporo-parietal regions.

been associated with this syndrome in only one case, which, however, lacked detailed documentation (Incorpora *et al.* 2002). Although some authors have reported a wide spectrum of interictal activities, including focal abnormalities and specific patterns similar to those observed in benign idiopathic partial epilepsy (Bergonzi *et al.* 1991) or Lennox-Gastaut Syndrome (Bergonzi *et al.* 1991, Musumeci *et al.* 1988), no data regarding ictal EEG activity have, as yet, been published.

In this case, we documented a very complex ictal pattern consisting of recruiting activity arising in the left posterior temporal regions, spreading to the homolateral hemisphere and triggering, probably through mesial fronto-occipital connections, an apparently independent ictal activity in the left frontal regions. This particular ictal pattern during the evolution of the seizures may be related to white matter fibre and pathway alterations detected in Fra-X patients by means of new neuroimaging techniques (Barnea-Goraly *et al.* 2003).

Ictal semeiology characterized by early lateralized motor signs is in accordance with the findings from previous cases (Musumeci *et al.* 1999, Musumeci *et al.* 1988), although a detailed clinical description is not, unfortunately, always available.

Another atypical feature of the case we describe is the fact that the seizures were drug-resistant, a finding reported in few previous cases (Incorpora *et al.* 2002, Bergonzi *et al.* 1991, Musumeci *et al.* 1988). Fra-X is, in fact, usually associated with partial epilepsy in which the seizures are drug-responsive.

In this patient, a well-localized structural malformation in the left mesial temporal lobe associated with an asymmetry of STVS was identified by means of the MRI study. This feature is not frequent in Fra-X patients, who tend rather to display structural abnormalities such as STVS or brain volumetric asymmetry (Eliez *et al.* 2001), hippocampal structure hyperdevelopment (Reiss *et al.* 1994), or grey matter/white matter ratio alterations predominantly involving the temporal lobe (Eliez *et al.* 2001, Reiss *et al.* 1994), basal ganglia (Eliez *et al.* 2001) and cerebellum (Mostofsky *et al.* 1998). No clear neuroimaging features supporting a well-defined malformation, such as focal or multifocal cortical dysplasia, have previously been described in the literature. The evidence of the reported structural alterations may partially explain some of the atypical clinical features of the case, especially drug-resistant seizures and the uncommon occurrence of SE.

Moreover, in our case the DWI images acquired during the SE showed a significant signal alteration located predominantly in the left fronto-temporo-parietal regions. As regards the brain regions affected by seizures, the DWI findings seem to be highly concordant with the EEG features, which show ictal activity arising from or involving the same regions. These data are in agreement with previously published results (Cole 2004), and thereby confirm diffusion signal changes related to reversible cerebral tissue edema during prolonged seizures. □

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