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Letter to the Editor

Rapidly fatal late-onset status epilepticus due to occult bi-frontal cortical dysplasia. A case report

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Focal cortical dysplasia
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Type Ic FCD

Focal cortical dysplasias (FCDs) are disorders of cortical development that usually present with childhood-onset, drug-resistant epilepsy. [1] Onset in adulthood has been described, but is considered rare. [1] Although high resolution MRI can detect most of FCDs, it is frequently unrevealing particularly in FCD type I. [1] Refractory status epilepticus (SE) due to "occult FCD" has been reported in four cases. [2] We describe a patient with late-onset refractory epilepsy who had type Ic occult FCD and recurrent partial SE with rapidly fatal outcome.

A previously healthy 49-year-old man came for a 3-month history of recurrent generalized tonic-clonic seizures, mainly occurring during sleep. Family history was negative for seizure disorders. Seizures occurred almost daily despite levetiracetam (1 g/day) and valproic acid (1.5 g/day). Two weeks later a marked increase of seizure frequency was observed and a prolonged video-EEG monitoring allowed to record recurrent frontal SE (Fig. 1a–d) clinically characterized by long-lasting (30–40 min) confusion with gestural and oral automatisms followed by left-sided or bilateral clonic–tonic–clonic seizures involving face and limbs. Following SE, patient had marked confusion and aggressiveness. Interictal neurological examination was normal. Interictal neuropsychological evaluation revealed mild visual-constructive apraxia. Brain CT scan and 3 Tesla MRI were uninformative. Total body CT scan was unremarkable. Routine laboratory analyses were normal. Cerebro spinal fluid (CSF) analysis showed the absence of oligo-clonal bands, with normal protein and cellular content. No serum antibodies against onco-neural antigens were found. Extensive serum tests for viral, bacterial and fungal infections, neoplastic serum markers (carcinoembryonic antigen, alpha-fetoprotein, Ca125, Ca19-9, Ca15-3), antibodies (Abs) to extractable-nuclear-antigen, anti-nuclear-Abs, cytoplasmic-antineutrophil cytoplasmic-Abs (cANCA), perinuclear-ANCA, anti-transglutaminase-Abs, anti-gliadin-Abs, anti-GAD-Abs, anti-VGKC-Abs, anti-NMDA-Abs, anti-GABA-Abs, anti-AMPA1-Abs, anti-AMPA2-Abs, anti-Gly-Abs and Quantiferon® were within normal limits. Thyroid hormones, antithyroid microsomal-Abs and antithyroid peroxidase-Abs were also normal. SE recurred with a daily frequency over the following months despite different combinations of antiepileptic drugs including carbamazepine (up to 1200 mg/day), phenytoin (up to 200 mg/day), phenobarbital (up to 300 mg/day), clobazam (10 mg/day), clonazepam (up to 7.5 mg/day), and topiramate (up to 400 mg/day). In the suspicion of seronegative autoimmune encephalopathy, i.v. boli of methylprednisolone (1 g/day for 5 days) and immunoglobulins (0.4 g/kg/day for 5 days) were unsuccessfully administered. The patient died five months after seizure onset because of cardiac arrest during convulsive SE. At brain autopsy, no macroscopic alterations were noted. Microscopic examination (Fig. 2, letters A to G) revealed abnormalities of both laminar and columnar cortical organizations, in keeping with type Ic FCD [3] in frontomesial cortices of both hemispheres. Of note, there were no lymphocytic infiltrates, as commonly seen during subacute encephalitis. Immunocytochemical analysis with parvalbumin (PV: an intracellular calcium-binding protein and a marker for some classes of GABAergic neurons) revealed a marked reduction of labelled cells in dysplastic cortices (Fig. 2: letters K, L) compared to normal regions (Fig. 2: letters H–J), as already described in type I FCDs. [4] Immunostaining for glial fibrillary acidic protein (GFAP) showed marked reactive gliosis in both white and deep gray matters of dysplastic cortices, especially around vessels (Fig. 2: letters M and N), presumably as a consequence of active epilepsy and SE. All other cortices, including hippocampi, were normal. A small calcified haemangioma, with no mass effect on adjacent parenchyma, was found in the cerebral falx. We herein describe a patient with rapidly fatal late-onset SE due to occult bi-frontal cortical dysplasia. Late-onset seizures have exceptionally been described in association with FCD and SE has been reported in a few cases. [1–3] Lack of visualization of many FCDs at MRI may delay diagnosis and surgical treatment. Indeed, life-threatening SE has been described in four patients with occult FCD [2] to whom surgery has been done as a "life-saving" procedure after a period of 1.5 to 6 years following the seizure onset. In the patient described here, both late-onset seizures and negative MRI findings did not allow a prompt diagnosis. Moreover, in this patient the rapid evolution of the clinical picture suggested a seronegative subacute encephalopathy and hindered to plan invasive pre-surgical recording. The reason of a delayed epilepsy onset in this patient remains obscure. It is suggested that FCD may remain clinically silent until stressors such as trauma, acute infection, metabolic, or even emotional abnormalities come into play by promoting de novo synaptogenesis with increased excitability of dysplastic lesion. [5] Animal studies showed a significant increase in the expression of GAP43 (a marker of newly formed synapses) protein in cortical and hippocampal regions of the dysplastic rat brains following a single injection of pentylenetetrazole. [5] We can speculate that an unknown second hit increased FCD excitability in the patient described here. Unfortunately, markers of de novo synaptogenesis could not be evaluated in his brain sample due to technical problems. We conclude that type I FCD should be considered in patients with late-onset refractory seizures with subacute life-threatening evolution, as it may require invasive recording aimed to surgery.

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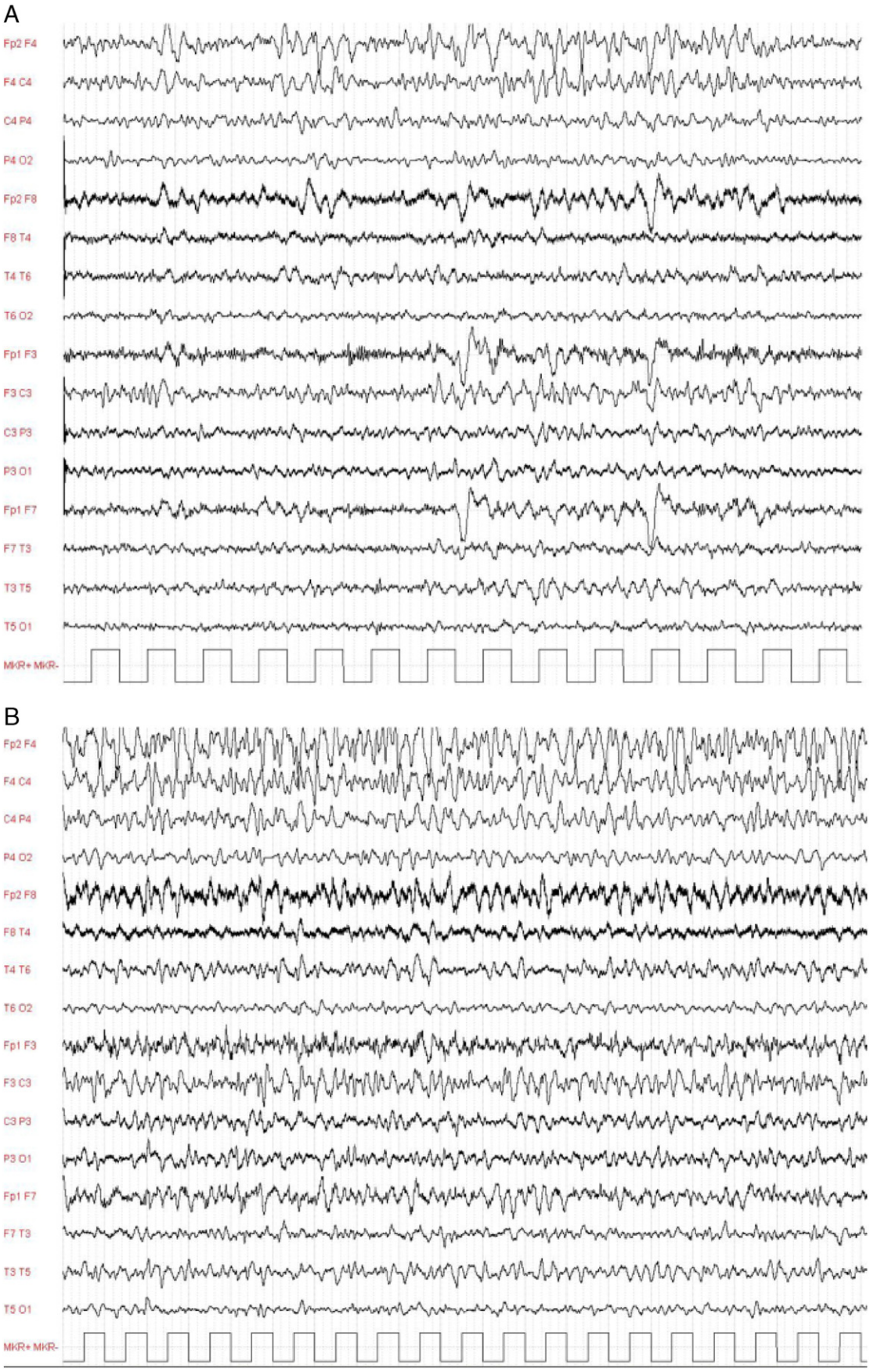

Fig. 1. At the beginning of the SE, while the patient was confused, EEG showed subtle intermittent rhythmic theta-delta activity mixed with spikes and polyspikes starting from the right frontal leads (A), that became overt and continuous after a few minutes (B). Diffuse polyspike and polyspike-wave discharges (C) were present during clonic fits. Post-ictal EEG showed mildly slow background activity and polymorphic delta waves over both frontal leads, more evident over right hemisphere.(**D**).