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Spontaneous seizure remission following status epilepticus in drug-resistant epilepsy due to focal cortical dysplasia

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Summary

We describe a patient with chronic pharmacoresistant epilepsy related to right parietal focal cortical dysplasia (FCD), who became seizure-free following an episode of convulsive status epilepticus (SE). Magnetic resonance imaging (MRI) and fludeoxyglucose positron emission tomography (FDG-PET) were performed before and after SE. Longitudinal MRI scans showed a stable appearance of the FCD with no new signal change. However, diffusion tensor imaging showed altered white matter fiber tract orientation in posterior cortices, especially in proximity to the lesion, at 3 years post-SE. FDG-PET showed more widespread hypometabolism 3 years after SE. The unusual occurrence of spontaneous seizure remission following SE in the context of FCD-related epilepsy, in association with neuroimaging evolution, suggests possible cerebral reorganization triggered by SE as a mechanism in this case.

Key words

Focal cortical dysplasia; status epilepticus; FDG-PET; diffusion tensor imaging

Introduction

Focal cortical dysplasias (FCD) are typically associated with epilepsy that often begins in childhood, the majority of cases proving to be pharmacoresistant¹. Because of poor response to antiepileptic drug (AED) treatment, surgery is often required, and spontaneous remission of epilepsy without surgery in these cases is very rare².

We report the case of a patient with chronic drug-resistant epilepsy related to focal cortical dysplasia, in whom an episode of convulsive status epilepticus (SE) was followed by complete and sustained remission of seizures, with longitudinal modifications in neuroimaging.

Clinical case

A 27-year-old right handed woman first presented seizures as an infant aged 8 months with eyelid clonus. Seizure expression evolved to altered contact and hypotonic falls by age 18 months. A period of seizure freedom was achieved with vigabatrin, taken until age 6 years. The patient remained seizure free off anti-epileptic drugs (AED) till aged 9 years, at which time seizures re-appeared, mainly nocturnal, characterised by unpleasant cephalic sensation, pressure in throat then loss of consciousness with hyperkinetic movements of all 4 limbs and ocular clonus, often progressing to secondary generalised tonic-clonic seizures (GTCS). Cerebral magnetic resonance imaging (MRI) performed at age 14 years in 2004 demonstrated right parietal focal cortical dysplasia (FCD), likely Type II (Fig 1A) and fludeoxyglucose positron emission tomography (FDG-PET) showed hypometabolism in the same region (Fig 2A). Because of resistance to AED polytherapy, presurgical evaluation was undertaken, including stereoelectroencephalography (SEEG) in 2010, which showed interictal discharges in relation to the FCD. However, despite prolonged SEEG recording during 3 weeks, only one spontaneous seizure was recorded, which showed some non-habitual semiological features and no clear electrophysiological change preceding clinical onset. The result of SEEG was therefore considered inconclusive and insufficient to permit surgical planning. Although a second SEEG exploration was subsequently proposed the patient declined this, and treatment was thereafter based on medical therapy alone. Transient improvement in seizure frequency and severity was seen during the 2

months following SIEEG, but her epilepsy remained active with seizure frequency of several nocturnal seizures per month, often secondary GTCS. She also developed fairly disabling migraines around this time. While baseline cognitive function was normal, her epilepsy severity required that stopping her university course. Multiple unsuccessful combinations of AED were tried, the most efficacious being topiramate and vigabatrin. Topiramate had a beneficial effect on migraine frequency. No period of seizure freedom of more than 14 days occurred between ages 9 and 24 years.

In 2013 at the age of 24 years, during a febrile illness, the patient presented a cluster of nocturnal GTCS evolving to generalized convulsive status epilepticus. This required emergency intensive care management with intubation and intravenous benzodiazepines and barbiturates, with resolution of seizures and extubation 12 hours later. Cerebral computerized tomography and cerebrospinal fluid examination were normal; no infectious cause was identified. Electroencephalography 48 hours after termination of SE showed persistent bilateral slow and spike activity, predominant on the right.

Following this episode of SE, the patient recovered rather gradually, complaining of ataxia and vertigo during a period of several weeks. The EEG in the month following SE remained altered with regards to baseline EEG, showing bilateral diffuse slow wave activity. Structural MRI was unchanged (Fig 1C). Clinical state and EEG abnormalities at this time were considered probably related to valproate therapy, which had been added after the episode of SE, with elevated plasma levels initially. At this point she was taking sodium valproate, topiramate, clobazam and vigabatrin. With AED dose reduction she gradually returned to her normal state with no neurological or cognitive sequelae and EEG normalized, at around 6 weeks after the episode of SE. Valproate was subsequently discontinued due to poor tolerance. In the 6 months following SE, the patient herself reduced and then stopped both vigabatrin and clobazam. In 2014, 1 year after SE, she also (without medical advice) reduced topiramate to 25mg per day, which remains her current regimen as monotherapy. No seizures have occurred since SE at 40 months' follow-up and the patient now works as a research assistant in a university laboratory. She reports noticeable improvement in quality of life, mood and cognitive function since post-SE seizure cessation and AED reduction. Cerebral MRI performed 36 months after SE (Fig1D) showed no structural change in relation to SE, and the appearance of the FCD remained similar to earlier imaging (fig 1A-C). However, diffusion tensor imaging (DTI) colored fractional

anisotropy map showed marked change in posterior cortex white matter tract orientation at 36 months post-SE compared to 1 month post-SE (fig 1D), suggesting cerebral reorganization in relation to the episode of SE. No DTI images were obtained prior to SE. Cerebral FDG-PET performed 36 months after SE showed alteration compared 6 years earlier (fig 2), with increased extent and severity of right posterior regional hypometabolism.

Discussion

This observation is a rare illustration of seizure remission occurring in a patient with chronic drug-resistant epilepsy due to radiologically confirmed FCD, in whom the temporal relation between episode of SE and seizure cessation suggests a likely causal role of SE.

Complete seizure remission lasting >12 months in chronic pharmaco-resistant epilepsy, including cases of FCD, may be seen in 4-10% of patients without surgery³ but usually occurs in a context of AED change². Radiologic findings in our patient indicated FCD (likely type II) as epilepsy etiology, with consistent regional PET changes⁴, and SEEG recording confirmed interictal abnormalities and subclinical discharges typical of this diagnosis⁵. Presence of FCD as etiology does not *per se* seem to infer greater or lesser chance of such spontaneous remission occurring, but likelihood of attaining subsequent seizure freedom has been shown to be rather decreased if SE occurs in adults during their epilepsy history². This presumably reflects more severe epilepsy cases, but may also indicate pathophysiological sequelae of SE with tendency to extension of epileptic networks, as has been shown in experimental models of brain circuitry⁶. Dysplastic cortex is intrinsically hyperexcitable, and cerebral networks associated with FCD are recognized to be highly epileptogenic and associated with electrophysiologic relationships that may be complex and unpredictable⁷. In patients with pharmaco-resistant epilepsy related to FCD, surgical excision of the whole dysplastic network is typically required in order to achieve seizure freedom⁷. The present observation of spontaneous seizure cessation in a case of FCD following SE is thus highly unusual, and poses intriguing questions as to possible mechanisms involved.

Following SE, MRI showed no change in the appearance of the dysplasia itself, nor new gray or white matter signal changes elsewhere, but changes in white matter tract orientation were demonstrated. A clear difference in white matter tract orientation in bilateral posterior cortices was seen in FA images between 1 month after SE and 3-years post-SE, suggesting an evolving process of cortical reorganization. While the lack of baseline FA data prior to SE limits somewhat the conclusions that can be drawn, the time course of these changes is highly suggestive of a causal role for SE. Diffusion tensor imaging (DTI) and fractional anisotropy (FA) have previously been used to demonstrate altered connectivity in subcortical tissue surrounding FCD⁸. Increased regional hypometabolism on FDG-PET compared to the pre-SE exam could also be in keeping with neuronal reorganization, although various factors such as cessation of seizure activity and AED reduction could equally contribute to the metabolic changes seen here.

The organisation of epilepsies related to FCD has been elucidated by SEEG studies that have led to recognition of particular electrophysiological signatures of interictal and ictal activity^{5,9}. In terms of network organization, signal analysis shows that in Type II FCD, the dysplasia plays a main role as a hub within the network, directly contributing to seizure initiation and propagation of seizures¹⁰. This typically lesion-centric network organization helps explain the often excellent surgical outcome in Type II FCD, whether radiologically visible or not, in contrast to some other cortical developmental pathologies (such as heterotopia), in which the epileptogenic network is often more widespread and not necessarily centered on the lesion.

While little human imaging data on long-term outcome of SE exist, MRI studies following SE in rat models show structural changes preferentially in cortex, amygdala and hippocampus, and changes in cerebral blood volume that are strikingly regional, involving specific layers of parietal and cingulate cortex as well as hippocampus, thalamus and striatum¹¹, suggesting different thresholds in different brain structures for expressing sequelae of SE. SE is well known to produce tissue damage that may lead to secondary epileptogenicity especially in hippocampus¹², and vascular changes during SE are likely to contribute to this complex process¹³. On the other hand the initial damage induced by SE can also enhance neuroplasticity as a recovery process¹⁴. A role for vascular density and blood brain barrier integrity in relation to epileptogenicity has been suggested based on observations from animal

models of epileptogenesis¹⁵, not only in terms of pathological effect but also in promoting beneficial outcome following cerebral injury¹⁴.

While clearly no conclusion can be drawn from this single case report, we might speculate that neuronal reorganization related to SE in the present case produced modulation of the dysplastic network that then led to seizure cessation, possibly via a process of cortical deafferentation, and perhaps augmented by higher sensitivity of parietal lobes to the effects of SE. The degree to which the imaging changes reported here reflect such a process is of course uncertain. However, this isolated and unusual case highlights the need for ongoing work into pathophysiological mechanisms involved in SE and epileptogenesis, including the impact of vascular and metabolic changes on epileptic networks.

Legends to Figures

Figure 1

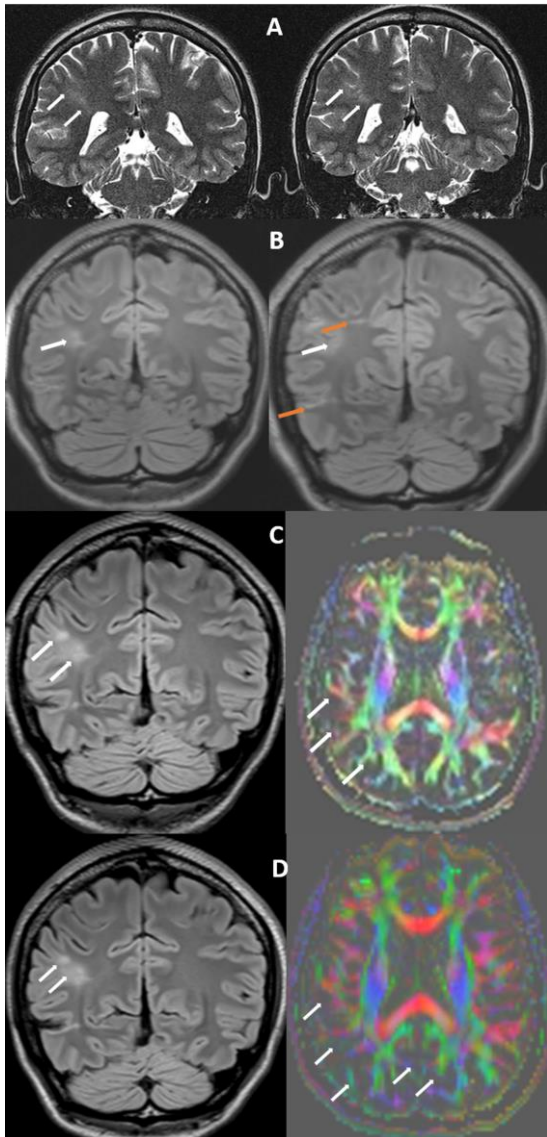


Fig 1 A. One year prior to SEEG: coronal T2 images showing focal cortical dysplasia characterized by slightly increased signal that extends from the cortex to the lateral ventricle (white arrows).

Fig 1B. Eighteen months after SEEG (before SE): coronal FLAIR images. Focal cortical dysplasia showing bright signal, similar to prior MRI (white arrow). Also note linear increased signal above the FCD, related to SEEG electrode (orange arrows)

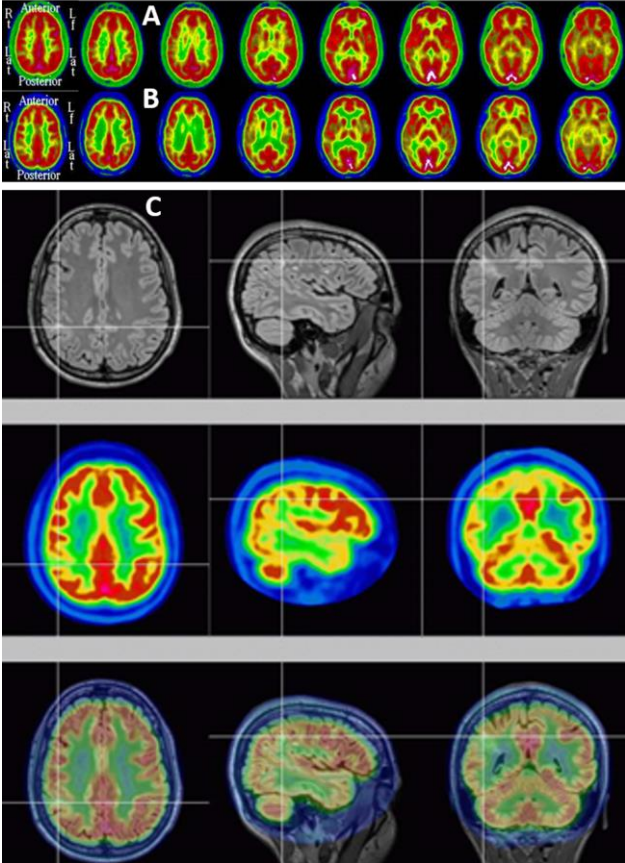
Figure 1C. One month after SE. Left image: coronal FLAIR image showing similar appearance of FCD. Right image: axial color FA image showing posterior asymmetry, with different orientation of white matter tracts underlying the cortical abnormality, compared to contralateral region.

Fig 1D. Three years after SE. Left image: coronal FLAIR image showing similar appearance of FCD. Right image: axial color FA image showing modification of the orientation of white matter tracts in right posterior cortex underlying the FCD but also contralateral mesial posterior cortex, compared to

the previous MRI shown in Fig 1C. Please note that colour intensity in figure 1D compared to the paler figure 1C is different simply because of technical changes in MRI acquisition in our center in the time period between these 2 scans. The important feature is the change in position of colored fibers, representing altered orientation of white matter tracts.

Figure 2

Axial brain 18-FDG PET performed before (Fig 2A) and 38 months after (Fig2B) the status epilepticus; 3-slices coregistration and fusion with 3F Flair MRI (Fig 2C). Focal inferior parietal PET hypometabolism was initially found, with more posterior diffuse abnormalities after the status epilepticus.



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Conflict of interest

None of the authors has any conflict of interest to disclose concerning the present publication.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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