■ Clinical commentary

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Epileptic Disorders

Focal status epilepticus may trigger relapse of primary angiitis of the CNS

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ABSTRACT

The role of neuroinflammation in epileptogenesis is extensively investigated, but short-term effects of seizures on established CNS pathologies are less studied and less predictable. We describe the case of a woman with previous recurrent episodes of focal cerebral haemorrhage of unknown cause who developed a pseudo-tumoural oedema triggered by provoked focal status epilepticus. A brain biopsy revealed that the underlying condition was primary angiitis of the CNS. Ictal-induced blood-brain barrier dysfunction allows the entry of water and inflammatory molecules that, in the context of CNS inflammatory diseases, may trigger a self-reinforcing process. Caution should be observed when tapering antiepileptic drugs in patients with such conditions.

Key words: focal status epilepticus, primary angiitis, CNS inflammatory disease

In the past two decades, there has been increasing evidence for a reciprocal causal link between brain inflammation and epilepsy. Firstly, seizures can induce neuroinflammation through a complex network implicating, among others, blood-brain barrier dysfunction (BBBD). Secondly, some of those neuroinflammatory pathways could play a pathogenic role in epileptogenesis and epilepsy comorbidities (*i.e.*, cognitive impairment and depression), but also in other conditions such as stroke and neurodegenerative, psychiatric and neuroinflammatory disorders [1]. Although long-term effects of neuroinflammation are well studied, little is known about the clinical short-term effects of seizures, especially in the case of established CNS pathologies.

Here, we describe a case of pseudo-tumoral oedema triggered by provoked focal status epilepticus (SE), ultimately leading to the diagnosis of primary angiitis of the CNS (PACNS), a rare vasculitis restricted to the CNS which affects women and men equally and can occur at almost every age (median: 50 years). The neurological manifestations are highly variable; seizures are present in less than 20% of the cases and are generally considered as a consequence of inflammatory relapses, contrary to our case [2].

Case study

A 54-year-old white woman, with a known smoking habit and hypertension, had three episodes of transient speech impairment and right clonic movements over a period of six months. Cerebral CT revealed recurrent subarachnoid haemorrhage in the same left parieto-occipital area. Repeated cerebral MRI

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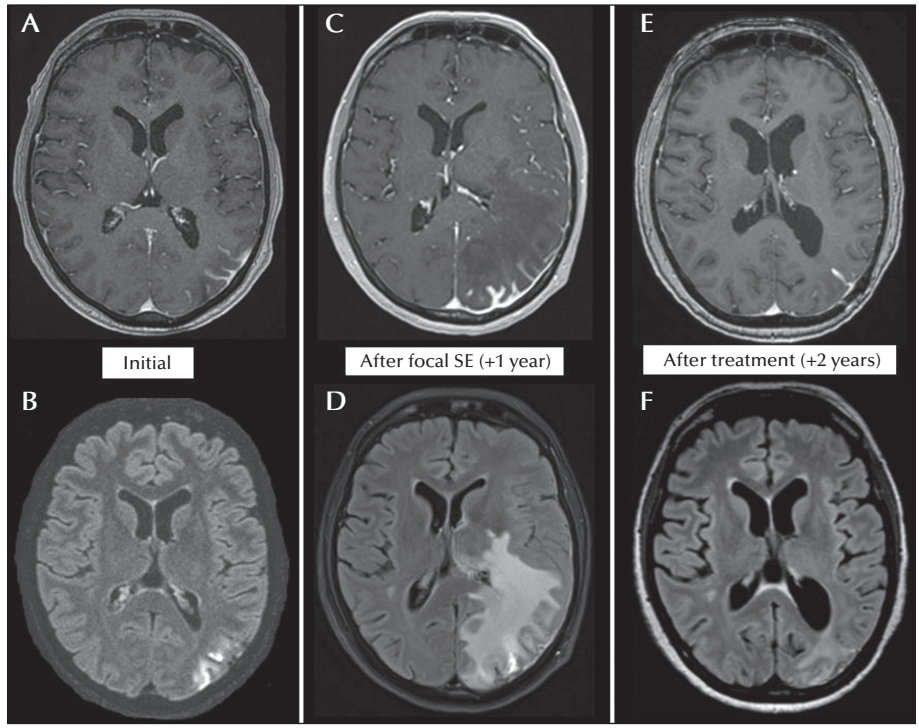
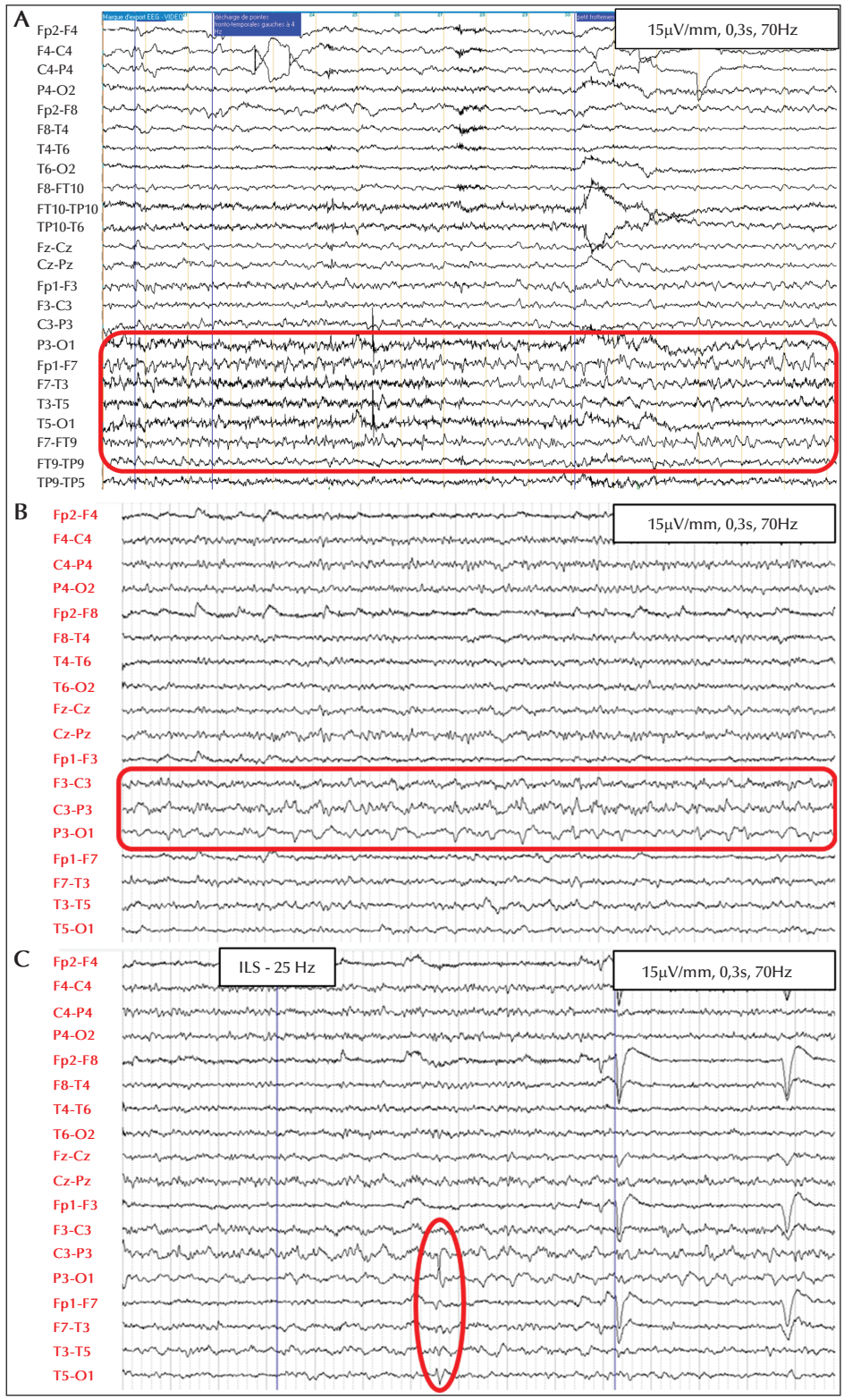
and angiographies showed no vascular abnormality but focal leptomeningeal enhancement of unknown aetiology (*figure 1A, B*). Secondary epilepsy was successfully managed with AEDs, namely levetiracetam at 3 g/day and lacosamide at 300 mg/day.

One year later, the patient reported unusual symptoms (prolonged tremor without impairment of awareness) suggestive of – and later confirmed – psychogenic non-epileptic seizures. However, during the diagnostic video-EEG monitoring, AED withdrawal induced prolonged focal SE for 30 minutes; the patient suddenly called for help, looking afraid and moaning, and had oro-alimentary automatisms and head deviation to the right, and finally right arm jerks and aphasia. EEG showed concomitant left fronto-temporal spike discharges (*figure 2A*). SE was stopped by intramuscular injection of midazolam (10 mg). After the SE, clinical examination revealed asomatognosia and right arm neglect, which were interpreted as post-ictal neurological impairments.

During the following weeks, the patient developed headache, psychomotor slowing and asthenia. One month after the focal SE, she was admitted to our hospital. Neurological examination revealed paraphasia, right homonymous hemianopia, brisk reflexes and right Babinski sign. EEG (*figure 2B, C*) revealed continuous left parietal slowing and interictal spikes during intermittent light stimulation. Cerebral CT showed no acute haemorrhage but a large area of hypodensity in the left parieto-occipito-temporal area. Brain MRI (*figure 1C, D*) revealed focal thickening and leptomeningeal enhancement of the left parieto-occipito-temporal area associated with large vasogenic oedema and local hemosiderosis. Inflammatory cerebral amyloid angiopathy (CAA) was suspected based on available clinical and radiological criteria [3]. The results of routine blood tests, work-up for infectious diseases, autoimmune and paraneoplastic screening and 18-fluorodeoxyglucose positron emission tomography (PET) were unremarkable. An analysis of the CSF demonstrated normal cellularity and protein and glucose levels but reduced levels of amyloid (242 pg/mL; normal >469 pg/mL) and specific oligoclonal bands. Amyloid PET showed increased uptake only within the haemorrhagic focus, which was therefore considered as leakage of the tracer rather than intrinsic amyloid deposition. A brain biopsy was performed.



■ **Figure 1.** Brain MRI (all views are based on similar slice location). Upper row:(A, C, E): post-contrast T1-weighted images showing an increase in enhanced meningeal thickening in the left parietal aera after focal SE (C), followed by a decrease after treatment with rituximab (E). Lower row (B, D, F): post-contrast FLAIR images (FLAIR multiplanar reconstruction in [B]) showing a large vasogenic oedema within brain parenchyma underlying meningeal changes after focal SE (D). A gliotic scar was present at the last control (F).



■ **Figure 2.** (A) EEG showing concomitant left fronto-temporal spike discharges during prolonged focal SE. (B, C) One month after the focal SE, EEG revealed continuous left parietal slowing and interictal spikes during intermittent light stimulation.

No amyloid deposits were found, excluding the hypothesis of inflammatory CAA. Histology showed chronic leptomeningitis associated with lymphocytic and neutrophilic vasculitis of various stages and multinucleated giant cells. Neither myeloproliferative disease nor infectious processes were found. Together, these features led to the diagnosis of PACNS.

The patient was treated with steroids (intravenous methylprednisolone, 1 g daily, followed by oral tapering) and cyclophosphamide (1 g monthly for six months), and gradually improved, but a relapse occurred during steroid tapering. The patient then received rituximab weekly for a month, and methylprednisolone was successfully tapered. At the one-year follow-up visit, the patient still had slight memory and speech impairment, but no relapse occurred. MRI demonstrated significant regression of the lesions (*figure 1E, F*).

Discussion

Our patient presented no symptoms for a year – except for confirmed psychogenic non-epileptic seizures – when prolonged focal SE provoked by AED withdrawal induced a rapid and significant clinical deterioration, sustained even after the focal SE resolved. The temporal sequence of events strongly suggests that iatrogenic focal SE triggered the inflammatory relapse. However, our study has an important limitation: no brain MRI was performed at the time of the video-EEG, thus the chronology of SE leading to a relapse of vasculitis could not be formally demonstrated, and the opposite chronology could not be totally ruled out.

MRI features of our patient (*i.e.*, leptomeningeal enhancement and infiltrative white matter processes) were highly suggestive of inflammatory CAA, also referred to as CAA-related inflammation (*CAA-ri*) and amyloid-β-related angiitis (*ABRA*); a specific subset of PACNS in which amyloid-β deposits cause an autoimmune reaction [2, 3]. However, no amyloid deposits were found on histopathological examination, excluding the diagnosis of inflammatory CAA. Pathological features led to the diagnosis of PACNS. A subtype of this disease with unilateral topography of the lesions has been recently described [4]. The clinical and radiological presentation of this case, along with intrathecal IgG synthesis, supports the presence of pro-inflammatory antigens abruptly released into the CNS during the focal SE.

In animal models, BBBD during the acute phase of SE is dynamic and time-dependent [5]. It has been shown that single seizures can induce BBBD. A recent prospective MRI-based study conducted on patients suffering from drug-resistant epilepsy demonstrated seizure-induced BBBD, temporally locked to the seizure and anatomically defined by the type of seizure, with more extended alterations in generalized tonic-clonic seizures [6]. Moreover, seizures can induce peri-ictal signal changes on MRI with topography involving, among others, unilateral cortex [7]. The pathophysiology remains unclear but in animal models, a decrease in the apparent diffusion coefficient (ADC) corresponds to mixed – cytotoxic and vasogenic – cerebral oedema, which can be induced by acute BBBD in seizures through the entry of water and blood proteins, among others [8, 9]. Interestingly, focal cerebral oedema – sometimes prolonged – following seizure and particularly focal SE, has been reported in some cases [10-12]. On the other hand, stroke and immune-mediated CNS diseases – including systemic lupus erythematous (SLE) – are known to cause BBBD [8, 13]. CNS vasculitis is also thought to induce BBBD, analogous to what is described in SLE [14]. We hypothesize that seizure-induced BBBD has more severe consequences when chronic CNS inflammatory conditions are present. In our case, cerebral oedema persisted after two months, which is longer than the average duration of post-ictal abnormalities [15]. Moreover, symptoms and oedema relapsed after the first attempt of steroid tapering, demonstrating that an inflammatory process, independent of ictal-induced cerebral oedema, was still active.

In conclusion, we describe a case of PACNS relapse with large vasogenic oedema probably triggered by provoked focal SE which, to our knowledge, has never been previously reported. Peri-ictal blood-brain barrier dysfunction allows the entry of water and inflammatory molecules into the CNS that may trigger a self-reinforcing process, especially in patients with underlying inflammatory conditions. Caution should be observed when tapering AEDs in patients with such conditions. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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The authors report no disclosures relevant to the manuscript.

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TEST YOURSELF

(1) Which of the following statements about neuroinflammation is incorrect?

A. Neuroinflammation plays a pathological role in various CNS disorders, including epilepsy
B. Neuroinflammation is typically associated with blood-brain barrier dysfunction
C. Neuroinflammation is an intrinsic normal brain response
D. None of the above

(2) Primary angiitis of the CNS can present with seizure in what percentage of the patients?

A. 10%
B. 20%
C. 30%
D. 40%

(3) Which of the following statements about inflammatory cerebral amyloid angiopathy is incorrect?

A. It is a subtype of primary angiitis of the CNS
B. It is characterized by an autoimmune reaction against amyloid deposits
C. It can induce pseudo-tumoural oedema
D. None of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.