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# Adult-onset Rasmussen encephalitis associated with focal cortical dysplasia

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**ABSTRACT** – Rasmussen encephalitis is a rare, devastating condition, typically presenting in childhood. Cases of adult-onset Rasmussen have also been described, but the clinical picture is less defined, rendering final diagnosis difficult. We present a case of adult-onset Rasmussen encephalitis with dual pathology, associated with focal cortical dysplasia and encephalitis. We interpreted the Rasmussen encephalitis to be caused by severe and continuous epileptic activity due to focal cortical dysplasia. The best therapeutic approach for such cases remains unclear.

**Key words:** adult-onset Rasmussen encephalitis, dual pathology, focal cortical dysplasia

## Case study

At the age of 17, this female patient presented a first episode of tonic-clonic seizures. The patient had no history of epilepsy, early-life trauma, or central nervous system infection. A consecutive work-up showed left fronto-centro-parietal epileptic activity *(figure 1)*. On MRI, hyperintense FLAIR lesions of the left frontal superior gyrus were identified *(figure 2)*. C11-methionine PET demonstrated no change in amino acid metabolism. The rest of the work-up (cerebrospinal fluid analysis and antineuronal antibody screening) was unremarkable.

Two months later, the patient developed motor status epilepticus with continuous jerks of the right hand, clinically corresponding to *epilepsia partialis continua* (EPC). Epileptic activity was refractory to levetiracetam, carbamazepine, topiramate, valproic acid, and lacosamide. Follow-up MRI showed a progression of the lesion *(figure 2)* and a second C11-methionine PET scan showed plurifocal hypermetabolism colocalizing with the hyperintense MRI lesions.

The first diagnostic hypothesis was a glioma of intermediate or high grade. Due to colocalization with eloquent motor cortex, a complete

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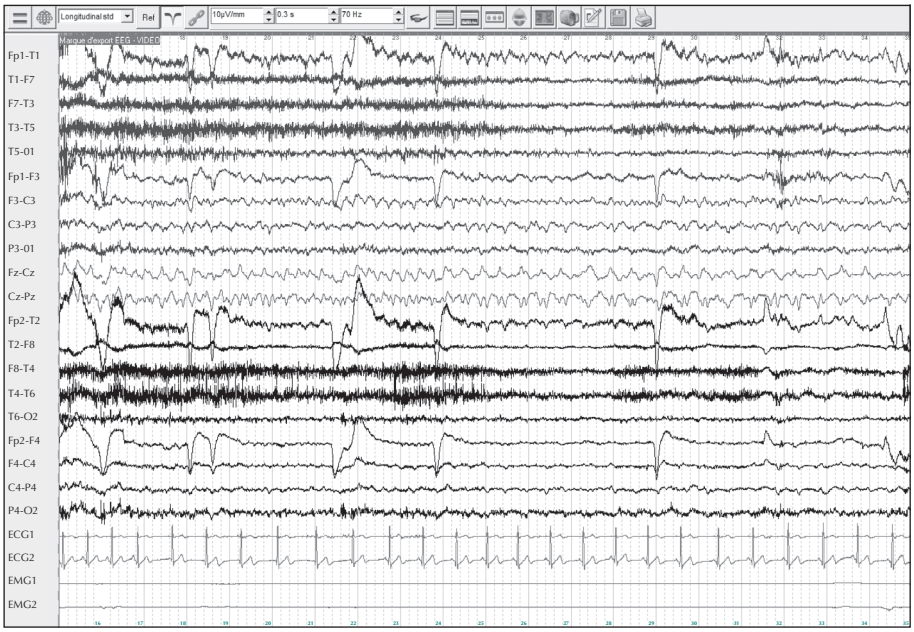


**Figure 1.** EEG showing left fronto-centro-parietal epileptic activity.

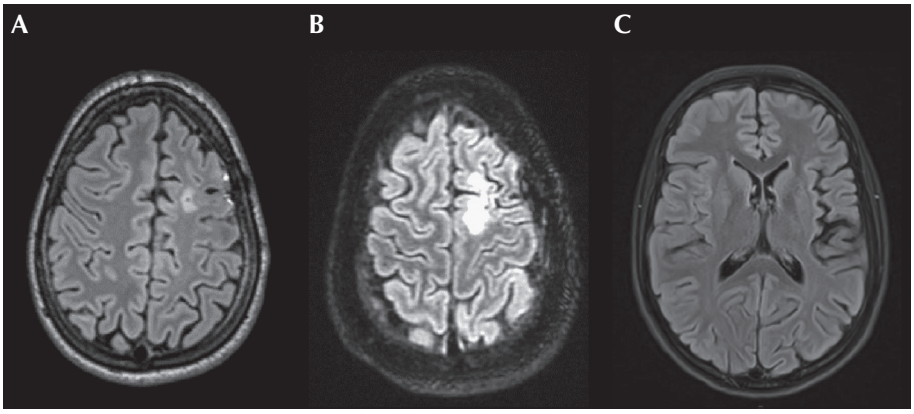


**Figure 2.** (A) Initial MRI showing hyperintense FLAIR lesions of the left frontal superior gyrus. (B) Second MRI showing progression of the lesions. (C) MRI showing left sylvian valley atrophy.

resection was not possible. A large biopsy of the lesion in the left frontal superior gyrus associated with multiple subpial transections was performed. Anatomo-pathological analysis revealed focal cortical dysplasia (FCD) 1b, *i.e.* FCD with abnormal tangential cortical lamination (Blümcke *et al.*, 2011). Furthermore, an abnormal loss of neurons with gliosis and neo-vascularization, as well as white matter with strong inflammatory, glial and macrophagic reaction, was described and immunostaining for CD3 showed a T-cell inflammatory reaction in the perivascular and parenchymal compartments of white matter. No B lymphocytes (CD20-), plasmocytes, or viral inclusion bodies were found *(figure 3)*. These features suggested the diagnosis of Rasmussen encephalitis.

After a brief improvement, the clinical status returned to initial severity. The patient received steroid-pulse treatment without clinical improvement. Follow-up MRI obtained four and ten months after surgery showed discrete atrophy of the sylvian valley *(figure 2)*, as well as a slight augmentation of peribiopsy hyperintensities.

The work-up was completed with fluorodesoxyglucose (FDG) PET (1.1 years after initial symptoms), showing left fronto-parietal, perisylvian, and superior

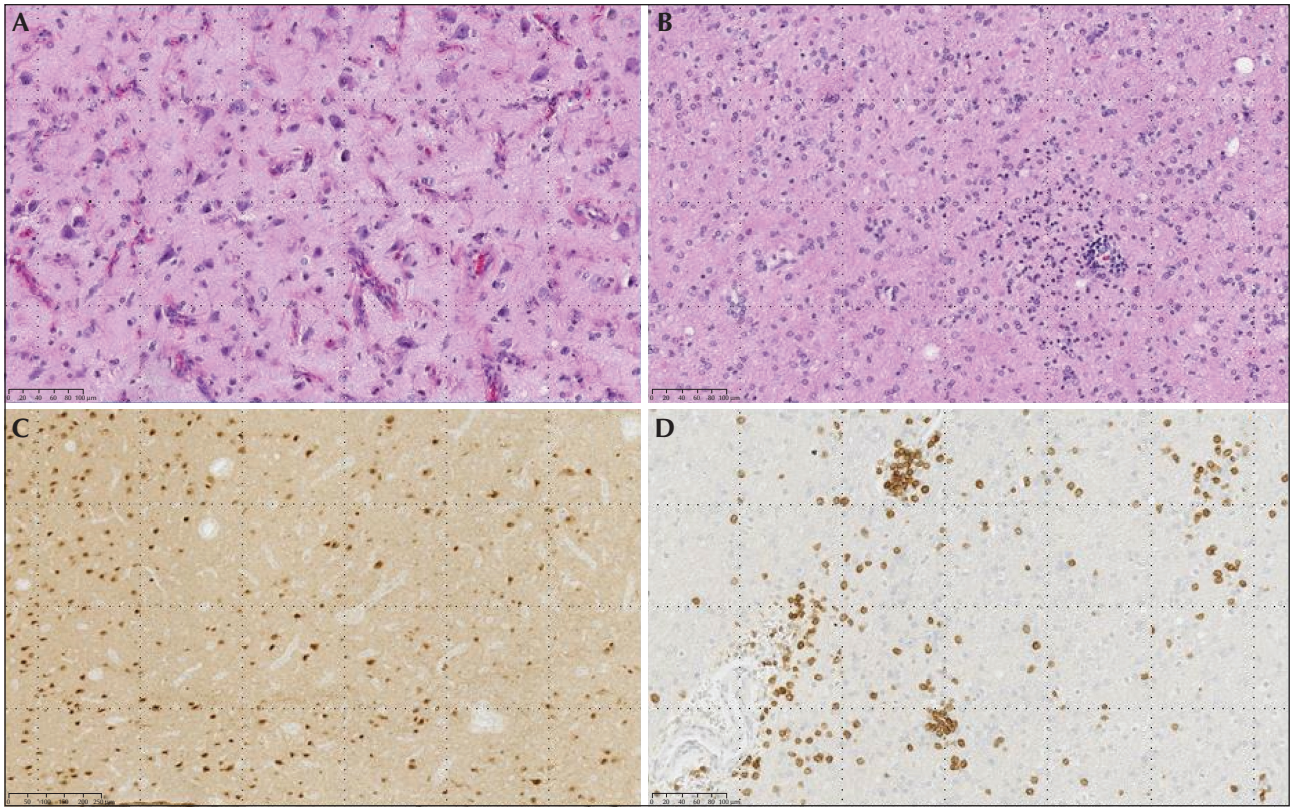


**Figure 3.** (A) Significant architectural disorganization (cortical dysplasia), loss of neurons, and glial and neo-vascular reaction (probable cicatricial Rasmussen disease) in the cortex. (B) White matter with inflammatory, glial, and macrophagic reactions. (C) NeuN staining confirms architectural disorganization and loss of neurons in the cortex. (D) Immunostaining for CD3 shows a T-cell inflammatory reaction in the white matter (peri-vascular and parenchyma).

temporal gyrus hypometabolism. The patient is currently under intravenous immunoglobulin therapy with no further clinical progression so far.

## Discussion

We present a case of EPC due to FCD associated with adult-onset Rasmussen encephalitis. Rasmussen encephalitis is an inflammatory brain disease of unknown aetiology affecting only one hemisphere, causing drug-resistant focal epilepsia/EPC, as well as progressive neurological and neuropsychological deficits. The prognosis is poor, related firstly to the persistence of seizures refractory to all antiepileptic medications, and secondly to severe encephalopathy. Hemispherectomy is the treatment of choice, allowing seizure freedom, cognitive stabilisation, and, in young patients, even motor recovery. Rasmussen encephalitis usually presents in childhood, however, cases of adult-onset have been described. In 2005, Bien *et al*. proposed diagnostic criteria combining clinical, radiological, EEG, and histological hallmarks (Bien *et al*., 2005). Presenting with EPC, progressive unihemisperic focal cortical atrophy, and histopathologically-proven T-cell-dominated encephalitis with activated microglial cells, our patient fulfilled clinical, radiological, and histopathological criteria for Rasmussen encephalitis. EEG criteria were not fulfilled; the EEG slowing remained focal and not hemispheric. However, in cases with typical radiological, clinical, and histopathological presentation, EEG criteria is not mandatory (Bien *et al*., 2005). The highly inflammatory presentation and the abnormal loss of neurons in the biopsy specimen, in combination with the evolution of the lesion based on two consecutive C11-methionine PET scans, the extension of the hypometabolic zone on FDG PET, as well as the clinical course with stabilisation under immunoglobulin therapy, are not explained by "simple" cortical dysplasia with secondary atrophy, but suggests dual pathology (FCD with Rasmussen encephalitis).

Two pathogenic processes may account for dual pathology. A first hypothesis assumes that the *primum movens* is the cortical lesion (Prayson, 2012). Ongoing epileptic activity caused by the cortical lesion disrupts

the blood/brain barrier, inducing a "vicious circle" of inflammation and parenchymal damage. In line with this hypothesis, the presence of an initial focal cortical lesion would also explain why Rasmussen encephalitis is unilateral in the vast majority of cases. The occurrence of inflammation in resected hippocampi of patients with temporal lobe epilepsy (Ravizza *et al.,* 2008), around tubers in patients with tuberous sclerosis (Boer *et al.,* 2008), and around epileptic cortical dysplasia (Boer *et al.,* 2006), as well as experiences based on rat and mice models in which the induction of seizures triggered inflammation, proves that epileptic activity can induce inflammation (Pernot *et al.,* 2011). Why FCD cases rarely evolve into Rasmussen encephalitis is unknown. EPC, tightly linked with Rasmussen encephalitis, typically occurs within the primary motor cortex. The primary motor cortex presents distinct characteristics of connectivity and excitability, and could present a unique risk for EPC. EPC could in turn provoke chronic inflammatory reactions. Furthermore, the patient's genetic background may modulate a dramatic inflammatory response, similar to that in Rasmussen encephalitis. The expression of antigens within the dysplastic cortex (for example, through particular major histocompatibility complex molecules) could activate CD8+ T cells, which are predominantly responsible for the immunological attack on neurons and astrocytes in Rasmussen encephalitis (Schwab *et al.,* 2009).

Based on a second hypothesis, it is proposed that inflammation induces neurogenesis and cortical disorganization, resulting in acquired FCD. The association between FCD and Rasmussen encephalitis, recognized by the ILAE classification as FCD type IIId, *i.e.* FCD in the presence of another epileptogenic brain lesion acquired during early-life trauma, ischaemic injury, and encephalitis (Blümcke *et al.,* 2011), reflects this theory. Our patient's early-life development was, however, unremarkable. Our interpretation is that the ongoing epileptic activity of EPC due to FCD was responsible for the onset of Rasmussen encephalitis, and therefore FCD Ib, and not IIId, was diagnosed.

To our knowledge, only few case reports distinguish between suspected pathomechanisms leading to dual pathology.

In three of seven cases of dual pathology reported by Takei *et al.,* the interval between seizure onset and surgical resection was less than six months, rendering the possibility of neurogenesis and appearance of dysplastic features unlikely (Takei *et al.,* 2010). Prayson *et al.* reported a patient who had undergone multiple surgical resections with an early diagnosis of FCD, before tissue was excised to diagnose Rasmussen encephalitis (Prayson, 2012). Both case reports support FCD as the *primum movens,* with Rasmussen encephalitis developing due to ongoing epileptic activity.

We have found no other case of dual pathology in adults. In children, dual pathology was mostly a coincidental histological finding. In patients with adult-onset Rasmussen encephalitis, surgical intervention is frequently not considered for two reasons. Firstly, while complete disconnection of the affected hemisphere is the most effective treatment in children, this may not be feasible for functional reasons in adults. Secondly, adult-onset Rasmussen encephalitis often presents with a milder phenotype and no surgical intervention is needed. In the absence of a histological sample, there is no proof of dual pathology and cases of adult-onset dual pathology may remain under-diagnosed.

Patients with adult-onset Rasmussen encephalitis are usually treated by immunomodulatory therapy. When FCD is present, it is unclear whether the therapeutic approach should be modified, *i.e.* resection of the dysplasia in combination with immunomodulatory therapy. More cases are needed to address this question.

## Conclusion

We present a rare case of adult-onset dual pathology associated with FCD and Rasmussen encephalitis. Our interpretation is that Rasmussen encephalitis was caused by severe and continuous epileptic activity due to FCD. The reasons for such a rare and catastrophic evolution of FCD are still unknown, as is the appropriate treatment regime for such cases. □

**Disclosures.**
None of the authors have any conflict of interest to declare.

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## TEST YOURSELF

(1) In what age group does Rasmussen encephalitis typically occur?

(2) Why is the association between FCD and Rasmussen encephalitis probably under-diagnosed in adults?

(3) What pathogenic features are suggested for FCD IIId, based on the ILAE classification?

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".*