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Multiphasic presentation of Rasmussen's encephalitis

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ABSTRACT – Rasmussen's encephalitis is a rare, chronic inflammatory disorder of unknown cause, characterised by drug-resistant focal epilepsy that may rarely present in adolescence or adulthood. We present a case of Rasmussen's encephalitis with prominent recurrent fluctuation in symptoms and well-documented fluctuating changes on MRI, adding to the spectrum of diversity of Rasmussen's encephalitis.

Key words: encephalitis, magnetic resonance imaging, fluctuation

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Rasmussen's encephalitis (RE) is a rare, chronic inflammatory disorder of unknown cause that most commonly presents in childhood. It typically presents with focal drug-resistant epilepsy, hemispheric atrophy, progressive intellectual decline, and neurological deficits (Bien *et al*., 2005; Varadkar *et al*., 2014). Characteristic MRI changes occur in the following sequence: swelling and hyperintense signal in affected areas of cortex and/or subcortical white matter and deep white matter on T2-weighted and fluid attenuation inversion recovery (FLAIR) images, normal volume and hyperintense signal, atrophy and hyperintense signal, and progressive atrophy and normal signal in the affected hemisphere (Bien *et al*., 2002; Yamazaki *et al*., 2011).

Atypical clinical presentations can be encountered. Individuals who present in adolescence or adulthood often have a less aggressive course and unusual features, such as occipital lobe involvement, bilateral

involvement, or absence of epilepsia partialis continua (Hart *et al.*, 1997; Gambardella *et al.*, 2008; Casciato *et al.*, 2013). Atypical MRI features of RE include improvement of hyperintense signal abnormalities without atrophy (one histologically-proven case described in the literature [Kim *et al.*, 2002]), improvement and one re-occurrence of hyperintense signal abnormalities (four histologically-proven cases described in the literature [Nakasu *et al.*, 1997; Yamazaki *et al.*, 2011]), or sustained increased signal on all follow-up MRI scans (one histologically-proven case described [Kim *et al.*, 2002]). We present an RE case with repeated clinical fluctuation, with associated fluctuating changes on MRI.

Case study

A previously healthy 16-year-old girl presented with two probable generalised tonic-clonic seizures (GTCS) within the preceding two months, a two-year history of episodes of multi-coloured flashing lights in the right superior temporal visual field associated with short-lasting mild throbbing headaches that had initially been treated as migraine, and fixed right superior homonymous quadrantanopia. Soon after the presentation, the frequency of the visual phenomena increased to several per day. She was referred to our centre 24 months after onset. The initial MRI scan under our care was considered normal, although a later re-evaluation raised the possibility of mild left hemisphere atrophy (*figure 1A*). Following the finding of bilateral runs of occipital interictal epileptiform discharges on EEG, a diagnosis of simple focal seizures with right upper quadrant visual symptoms was made elsewhere. Treatment with carbamazepine was started, but was not tolerated. However, the frequency of simple focal seizures returned to baseline (monthly episodes) without antiepileptic medication. Thirty-seven months after the initial presentation, GTCS re-occurred. Treatment with levetiracetam was started. Over the next 28 months, she had several GTCS, mainly associated with poor sleep and non-adherence. Simple focal seizures occurred in clusters perimenstrually, eventually increasing to several per day. A series of MRI scans was performed over this period, initially *(figure 1B)* without any changes in comparison with the baseline scan. However, following a bout of increased GTCS frequency, high-intensity lesions appeared in the cortex of the left precuneus, with some extension to the cuneus along the left parieto-occipital sulcus and extension along the superior bank of the calcarine cortex (*figure 1C*). There was no pathological contrast enhancement. The seizures then settled without major changes in treatment. Along with clinical improvement, there was almost complete resolution of the hyperintensity changes in the left occipital lobe on MRI, leaving behind a small area of volume loss with persistent signal change in the left occipital lobe (*compare figure 1E and 1D*). The long-standing right-sided homonymous quadrantanopia was confirmed with Humphrey perimetry at month 47. The visual field defect progressed to right-sided hemianopia with macular sparing (*figure 1K-M*).

There were two further exacerbations of seizures: in month 70 after the initial presentation and in months 77 to 81, followed by improvement to baseline on both occasions. During the last exacerbation, she developed brief episodes of sensory abnormality and jerking of her right leg, sometimes associated with inability to move the leg, in addition to her habitual simple focal seizures and GTCS. Around this time, the right-sided hemianopia was noted to be complete. MRI during the exacerbation at month 70 showed a new distribution of sub-cortical and cortical changes in the left occipital lobe (*figure 1F*), with progression over the next two months, followed by almost complete resolution, apart from the fixed area of parenchymal volume loss along the left calcarine sulcus (*figure 1G*). In month 78, there was a further exacerbation and redistribution of the hyperintensity changes on MRI, which improved to some extent by month 85, when MRI showed less extensive T2 hyperintense signal, involving predominantly white matter of the cuneus and precuneus (*figure 1H and I*; the latter scan also shows linear artefact related to neurosurgical biopsy; see below). EEG showed long runs of slow waves in the left occipital region. Perimetry improved by month 84, not thought to be a practice effect (*figure 1O*).

Neurological examination was normal throughout the course of the disease, with the exception of the visual field defect. The following tests were normal or negative: full blood count, electrolytes, liver function tests, thyroid function, vitamin B12, folate, ANCA, ANA, rheumatoid factor, coeliac screen, and antineuronal antibodies (anti-Hu, Yo, Ri, CV2, amphiphysin, and Tr). Lumbar puncture at month 68 showed unmatched oligoclonal bands in the CSF, with normal cell counts. Sequencing of *POLG*, targeted mutation screening of *PEO1,* and testing for the MELAS mutation (m.3243A>G) in blood were negative.

She underwent brain biopsy at month 81. The biopsy sample was taken from the area immediately above the left occipito-parietal sulcus. Histological sections were examined by four expert epilepsy neuropathologists (MT, TJ, IB, and EA). The predominant pathological process was inflammation involving the grey and white matter, with prominent T cells and microglial aggregates, occasional neuronophagia, and some mild inflammation in the dura (*figure 2*). There was some

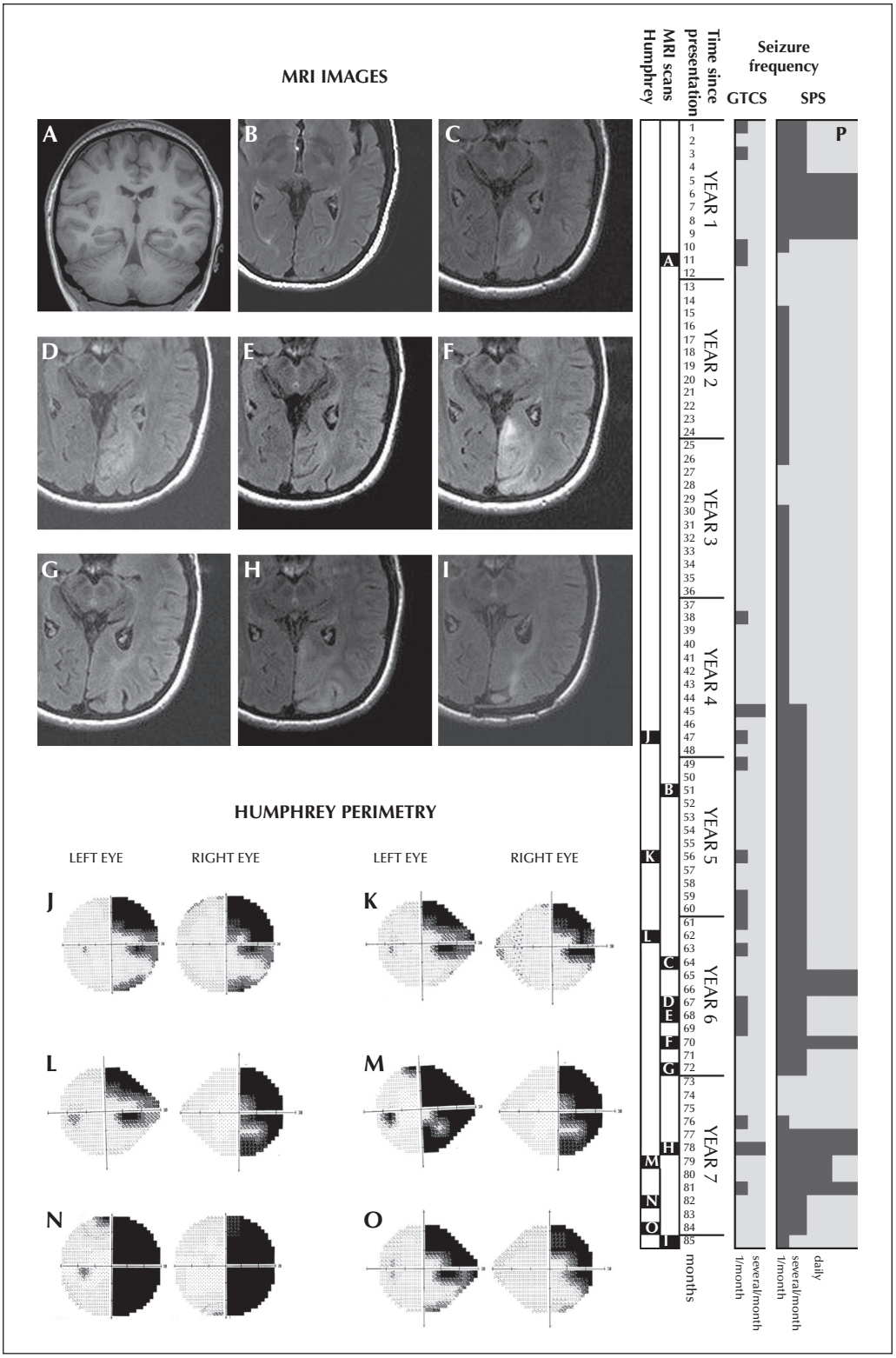

Figure 1. Normal baseline MRI (T1 coronal image shown; axial images were not available; MRI parameters: strength: 3T; TE: 3.072 ms; TR: 7.708 ms) (A). Fluctuating MRI hyperintensities on FLAIR (fluid attenuated inversion recovery; MRI parameters: strength: 3T; TE: 141.9 ms; TR: 1100 ms; TI: 2250 ms) images (B-I); visual field changes detected with Humphrey perimetry (J-O). Timeline showing GTCS (generalised tonic-clonic seizures) and SPS (simple focal seizures) frequency changes in time (P). *Seizure frequency scale is not in proportion.

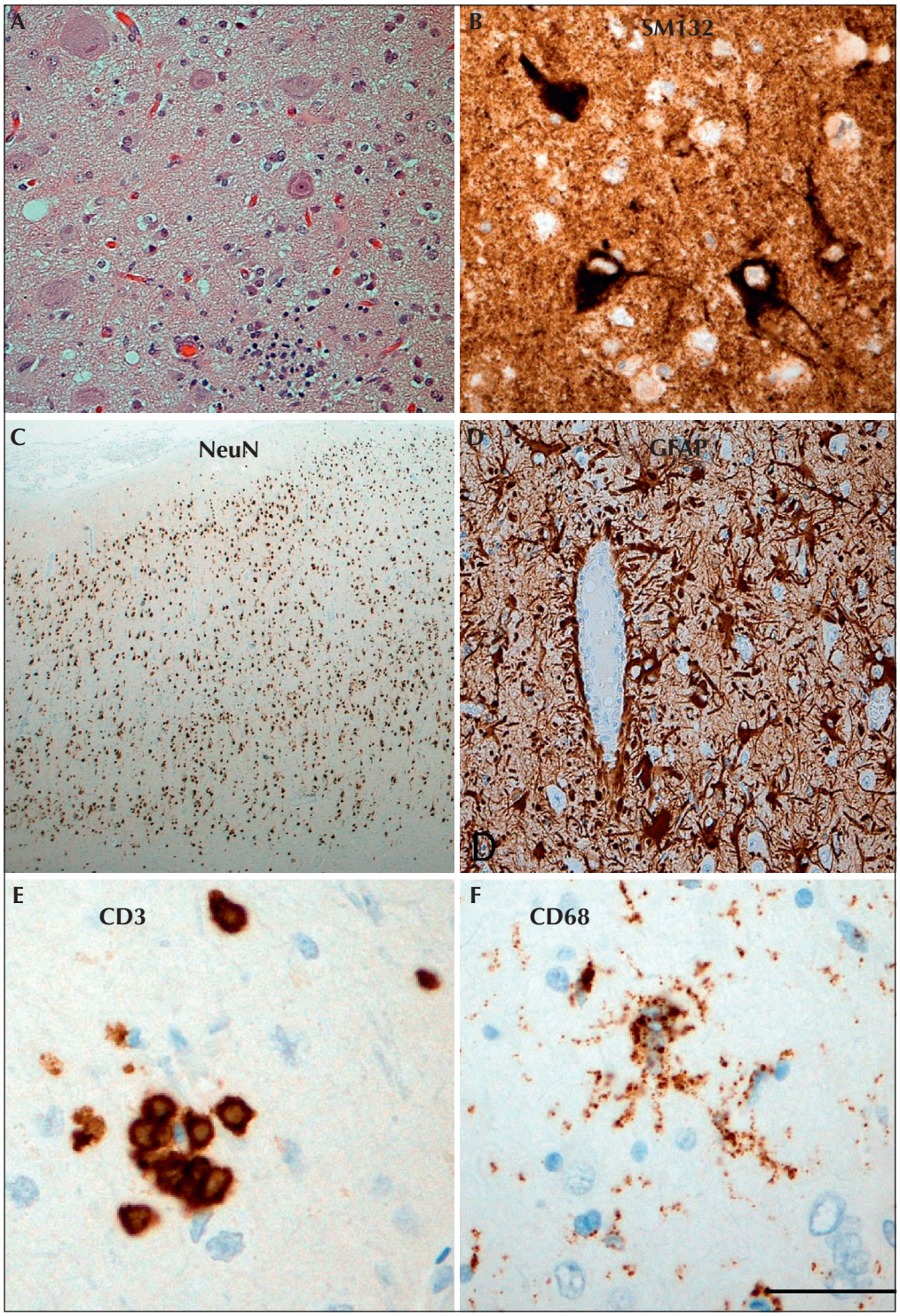

Figure 2. Histological changes in brain biopsy sample. (A) Cortex showed scattered hypertrophic neurones in all laminae, reactive astrocytes (but no balloon cells) and focal aggregates of lymphocytes and microglia, highlighting possible neuronophagia (H&E stain). (B) Neurofilament staining (SMI32) showed enlarged and distorted pyramidal cells within the cortical plate. (C) The impression of NeuN stain was of overall preservation of the six-layered cortex with superimposed changes; this picture is not typical for FCD type IIb. (D) The GFAP stain showed a pan-cortical and white matter-reactive cellular gliosis; there was no evidence of laminar gliosis or balloon cells. This pattern suggests a subacute glial response. (E) Inflammatory markers such as CD3 showed increased, focal infiltrates of small T cells around vessels and small aggregates in the parenchyma. (F) Microglial markers (CD68) also highlighted clusters of microglial cells within the cortex.
Bar is equivalent to approximately 50 microns in (B), (E), and (F); 120 microns in (A) and (D); and 250 microns in (C).

disruption in the cytoarchitecture, but the primary process was inflammatory, compatible with RE. She met three of the "Part A" criteria for RE, sufficient to establish the clinical diagnosis (Bien *et al*., 2005). Taking into account the clinical diagnosis and supporting histological findings, a diagnosis of RE was made.

Discussion

Repeated cycles of fluctuation of seizure frequency and accompanying marked fluctuation of signal hyperintensities on MRI T2 FLAIR images were the most striking features in this case. We were able to document the evolution of seizures and hyperintense lesions over a period of seven years. Whilst typically in RE there is a linear progression from hyperintense changes to atrophy, cases where hyperintense lesions on MRI regress once and re-appear after several years have been described in the literature (Yamazaki *et al*., 2011). In our case, we observed three cycles of appearance and regression of hyperintense MRI changes, which has not been described before.

Yamazaki *et al*. described five cases of RE where the hyperintense MRI lesions regressed once and re-appeared after 70.8±38.0 months, which was concordant with improvement and worsening of seizures, similar to our observations. Only two subjects had epilepsia partialis continua. Three of their cases were histologically-proven and successfully treated with surgery. In a further case series, two out of 11 subjects were found to have fluctuating hyperintense MRI lesions, although the chronological details and histology data were not given (Pradeep *et al*., 2014). One case where the hyperintense changes regressed and re-appeared in relation to immunosuppressive treatment has been described (Nakasu *et al*., 1997). We observed fluctuation for a longer period of time and clearly documented three full cycles of exacerbation and regression (but not complete remission) of hyperintense MRI changes. Fluctuation probably reflects the inflammatory nature of RE (Yamazaki *et al*., 2011). No triggering factors (such as infection) for the exacerbations were identified.

The baseline MRI scan under our care was performed more than two years after the onset of visual phenomena and one month after the first seizure exacerbation had resolved. Later re-evaluation, after the onset of signal changes on subsequent MRI, suggested possible mild left cerebral hemisphere atrophy in this first scan. One possible explanation for this finding is that the pathological process had started long before the scan was undertaken and might have been more extensive than suggested by the left occipital symptoms. The first scan was not undertaken at the time when the seizure frequency was high, but when the seizure frequency had already returned to baseline. We can only speculate whether any hyperintense changes may have been present at the time of the first seizure frequency peak.

Whilst there was a long period of better seizure control between the first and the second exacerbation of seizures, the subsequent exacerbations occurred in quick succession, which could possibly imply that the underlying pathological process was less pronounced in the first years, but became more active later.

In line with the fluctuating nature of the MRI changes, a broad spectrum of possible causes was considered, including infectious, neoplastic, paraneoplastic, and mitochondrial causes. Peri-ictal signal change was also considered (Yaffe *et al*., 1995). However, not all MRIs that demonstrated hyperintense changes followed overt clusters of seizures, and atrophy would not be consistent with this diagnosis. There were slight cytoarchitectural abnormalities, and a diagnosis of focal cortical dysplasia (FCD) was also considered as a secondary pathology (Blümcke *et al*., 2011). In a recent series of patients with RE, FCD (type IIId) was found in four cases (Wang *et al*., 2013). There were no balloon cells to support a diagnosis of a primary FCD (type IIb). T-lymphocytic infiltrates constituted the main histological finding, and a firm consensus diagnosis of RE was made by four independent expert neuropathologists.

In conclusion, linear clinical and MRI staging (Bien *et al*., 2002) may not encompass the full spectrum of patterns of change in RE. A number of cases with a clinical course that differs from the classical linear development of changes have been described. A less aggressive course with one or more cycles of exacerbation and remission of seizures and MRI changes can be encountered. A diagnosis of RE should be considered with such recurrent cycles of improvement and exacerbation of clinical and imaging features. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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References

Bien CG, Urbach H, Deckert M, *et al*. Diagnosis and staging of Rasmussen's encephalitis by serial MRI and histopathology. *Neurology* 2002; 58(2): 250-7.

Bien CG, Granata T, Antozzi C, *et al*. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain* 2005; 128(3): 454-71.

Blümcke I, Thom M, Aronica E, *et al*. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 2011; 52(1): 158-74.

Casciato S, Di Bonaventura C, Fattouch J, *et al*. Extrarolandic electroclinical findings in the evolution of adult-onset Rasmussen's encephalitis. *Epilepsy Behav* 2013; 28(3): 467-73.

Gambardella A, Andremann S, Shorvon S. Limited chronic focal encephalitis: another variant of Rasmussen syndrome? *Neurology* 2008; 70(5): 374-7.

Hart YM, Andremann F, Fish DR, *et al*. Chronic encephalitis and epilepsy in adults and adolescents: a variant of Rasmussen's syndrome? *Neurology* 1997; 48(2): 418-24.

Kim SJ, Park YD, Pillai JJ, *et al*. A longitudinal MRI study in children with Rasmussen syndrome. *Pediatr Neurol* 2002; 27(4): 282-8.

Nakasu S, Isozumi T, Yamamoto A, *et al*. Serial magnetic resonance imaging findings of Rasmussen's encephalitis-case report. *Neurol Med Chir (Tokyo)* 1997; 37(12): 924-8.

Pradeep K, Sinha S, Saini J, *et al*. Evolution of MRI changes in Rasmussen's encephalitis. *Acta Neurol Scand* 2014; 130(4): 253-9.

Varadkar S, Bien CG, Kruse CA, *et al*. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. *Lancet Neurol* 2014; 13(2): 195-205.

Wang D, Blümcke I, Gui Q, *et al*. Clinico-pathological investigations of Rasmussen encephalitis suggest multifocal disease progression and associated focal cortical dysplasia. *Epileptic Disord* 2013; 15(1): 32-43.

Yaffe K, Ferriero D, Barkovich AJ, *et al*. Reversible MRI abnormalities following seizures. *Neurology* 1995; 45(1): 104-8.

Yamazaki E, Takahashi Y, Akasaka N, *et al*. Temporal changes in brain MRI findings in Rasmussen syndrome. *Epileptic Disord* 2011; 13(3): 229-39.

TEST YOURSELF

(1) What is the typical clinical course of RE?

(2) What are the characteristic MRI changes in RE?

(3) Is the clinical course of RE always monophasic?

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".