Clinical commentary

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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

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, eventu-
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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).
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 had 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 epilepsy 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


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**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.”*