■ Clinical vignette

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Epileptic Disorders

Cyclic seizures in lethal neonatal rigidity and multifocal seizure syndrome: expanding the phenotype of a rare entity

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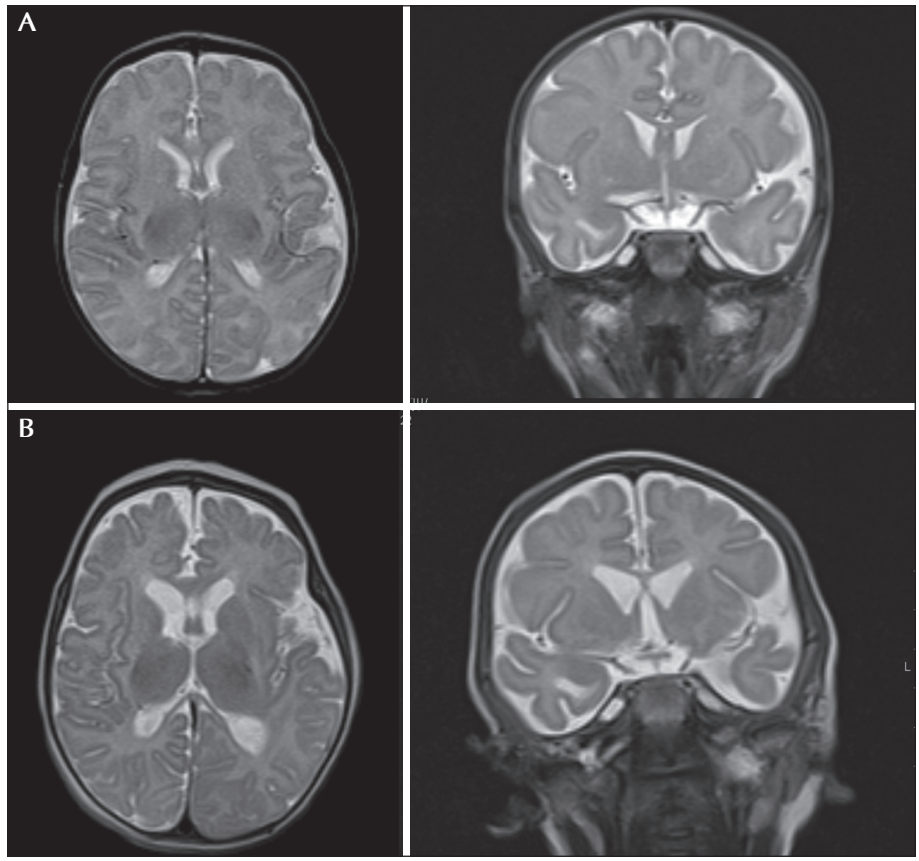
A 14-day-old male, born at term after an uneventful delivery, was admitted to our hospital due to feeding difficulties, failure to thrive and a 9% weight loss in relation to the birth weight. Family history was unremarkable, with no parental consanguinity. Physical examination revealed microcephaly, retrognathia, appendicular hypertonia and hyperreflexia. During admission, frequent focal myoclonus was noticed, occurring spontaneously and involving the head or any of the limbs. Continuous video-EEG monitoring (cEEG) showed an immature pattern with *tracé descontinue* during quiet sleep, independent bihemispheric epileptiform activity and electrographic seizures arising from the central regions. Myoclonic jerks did not show a specific electrographic correlation. We started levetiracetam and clonazepam with slight improvement. Brain MRI was normal (*figure 1A*). An extensive complementary study including cerebrospinal fluid analysis and cardiovascular and ophthalmological examinations were normal. At two months of age, he was readmitted maintaining frequent myoclonic jerks of the limbs, eyelids and head that were associated with cyanosis and desaturation. A repeat 12-hour cEEG showed a continuous pattern with mixed frequencies, without reactivity, posterior rhythm or differentiated transients of sleep, with multifocal epileptiform activity predominantly over the posterior regions (*figure 2A*) and multiple seizures grouped in two main clusters, with poor clinical correlation. The initial ictal pattern was localized to the left or right posterior quadrants, sometimes with contralateral or diffuse spreading (*figure 2B*). Occasionally, we could see overlapping seizures in both hemispheres. Longer seizures were associated, at the end, with bilateral independent periodic discharges (BLPDs) and hemispheric or generalized suppression. The amplitude-integrated EEG (aEEG) depicted a cyclic seizure (CS) pattern, meaning seizure re-occurrence at relatively regular intervals (mean seizure duration was 7 minutes and inter-seizure interval was 6 minutes) (*figure 2B*). A second MRI at 2.5 months of age revealed diffuse brain atrophy and a thin corpus callosum, without focal lesions (*figure 1B*). Genetic analysis identified a homozygous pathogenic frameshift variant, c.638dupA (p.Val214Glyfs*189), in exon 5 of the *BRAT1* gene, confirming the diagnosis of lethal neonatal rigidity and multifocal seizure syndrome (RMFSL). Both parents were asymptomatic and heterozygous for this variant.

He was readmitted at three months with increasing seizure frequency. Phenobarbital was added with a partial response. However, the patient died after a respiratory infection and multiorgan failure.



■ **Figure 1.** Brain MRI (axial and coronal T2-weighted images) at one month of age, described as normal (A), and at 2.5 months of age, showing generalized brain atrophy (B).

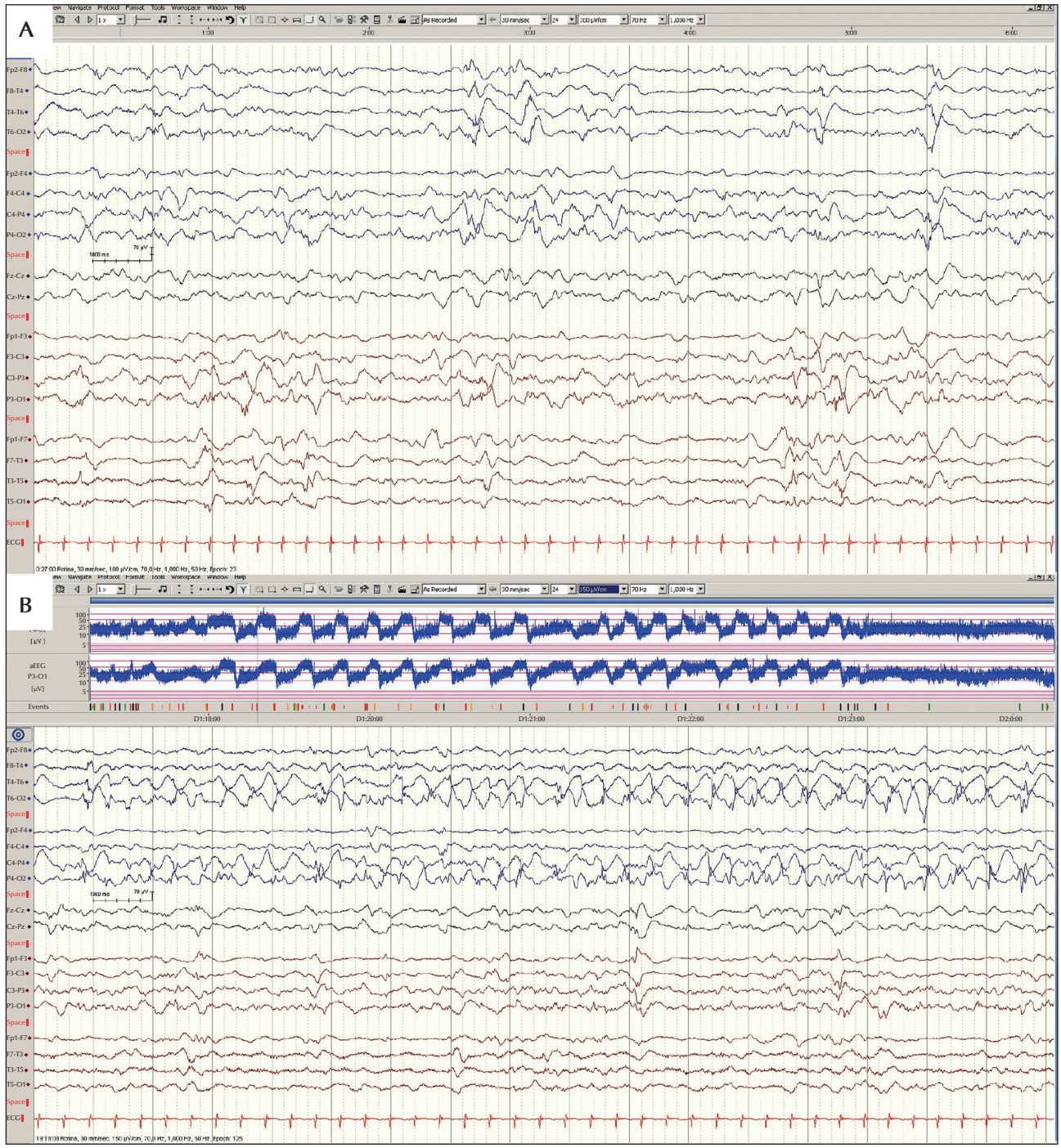
We describe the first Portuguese patient with a diagnosis of RMFSL, due to a homozygous variant in the *BRAT1* gene, who presented a CS pattern, not previously associated with this syndrome. He shared many of the reported clinical characteristics, namely neonatal onset of drug-resistant epilepsy, microcephaly, hypertonia, hyperreflexia, feeding difficulties and death in the first months of life. Findings of diffuse atrophy on brain MRI are common [1-3].

Myoclonic seizures are consistently reported as the main seizure type, although clonic, tonic, generalized tonic-clonic and events of apnoea and desaturation have also been described [4-7]. Concerning EEG, reported abnormalities are slow, low-voltage background or burst-suppression, focal or generalized epileptiform activity and multifocal seizures [1-4]. Recently, a severe syndrome of epilepsy of infancy with migrating focal seizures was recognized in RMFSL patients [6-8].

In our case, EEG findings were consistent with an epileptic encephalopathy with frequent seizures shifting between hemispheres or overlapping, as in migrating focal seizures, although a clinical correlation was weak. Moreover, seizures occurred at consistently regular intervals, in a cyclic pattern, which is a rare finding in paediatric age. This feature was noticed based on cEEG, and was easily documented with the aid of a quantitative EEG technique, such as aEEG.

Recently, two series with CS in critically ill patients were published. The pathophysiology is unknown but some authors argue that CS can be a form of SE in which endogenous antiepileptic mechanisms are only transiently effective [9]. Others implicate the subcortical structures in CS, speculating that ictal activity might persist in deep structures, but terminate in the cortex and then spread into it later [10].

In the present case, the epilepsy and greater seizure burden as well as the neurodegenerative process itself might explain the clinical course and mortality during the first months of life. It is unclear, however, whether the CS may cause additional neuronal injury with a subsequent effect on outcome or whether it is merely a marker of disease severity. Extensive molecular and pathological studies combined with electroclinical data might help answering this question in the future. ■



■ **Figure 2.** EEG samples in bipolar montage with electrodes placed according to the international 10-20 system; sensitivity: 7uV/mm, band-pass filter: 1-70 Hz, 30mm/sec. (A) Interictal: multifocal epileptiform activity (spikes, polyspikes and sharp waves) predominantly over the posterior regions. (B) Ictal: seizure onset with rhythmic delta activity in the right posterior quadrant. In the upper part of the image, the aEEG (P3-O1, P4-O2) shows the cyclic seizure pattern (frequency: 5/hour; inter-seizure interval: 6 minutes); ongoing seizures correspond to the build-up of voltage over 25 µV, and at the end of the seizure, suppression can be seen.

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

Disclosures.
None of the authors declare any conflicts of interest.

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TEST YOURSELF

(1) What are the main clinical findings in lethal neonatal rigidity and multifocal seizure syndrome (RMFSL)?

(2) What types of seizures are typically described with RMFSL?

(3) What are the main EEG findings?

(4) Which feature of the ictal pattern was highlighted in this case?

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