

Atypical presentation in Rasmussen encephalitis: delayed late-onset periodic epileptic spasms

Taíssa P.F. Ferrari¹, Ana P.A. Hamad¹,
Luís Otávio S.F. Caboclo¹, Ricardo S. Centeno¹,
Ana Luiza Zaninotto¹, Monica Scattolin¹,
Henrique Carrete Junior², Carmem L.P. Lancellotti³,
Elza Márcia T. Yacubian¹

¹ Departamento de Neurologia e Neurocirurgia, Universidade Federal de São Paulo

² Departamento de Diagnóstico por Imagem, Universidade Federal de São Paulo

³ Departamento de Patologia, Santa Casa de São Paulo, São Paulo, Brazil

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ABSTRACT – A five-and-a-half-year-old girl started experiencing progressive left hemiparesis at age two and a half years. At age five years and four months she started presenting clusters of asymmetric periodic epileptic spasms with no hypsarrhythmia. The ictal EEG showed periodic, constant and stereotyped complexes. Serial brain imaging revealed progressive atrophy of the right hemisphere with increased T2 signal on MRI. She underwent a right hemispherotomy, and histological examination showed signs of inflammation and features of focal cortical dysplasia (FCD). She has been seizure-free for 16 months. This case is unique in the following aspects: the presence of typical Rasmussen encephalitis features of progressive unilateral brain involvement without seizures, a delay of almost three years prior to seizure onset; an atypical seizure type presentation with periodic epileptic spasms and the presence of FCD associated with inflammatory changes. [Published with video sequences]

Key words: Rasmussen encephalitis, late-onset spasms, epileptic spasms, periodic spasms, focal cortical dysplasia



Correspondence:

T.P.F. Ferrari
Unidade de Pesquisa e Tratamento de
Epilepsia (UNIPETE),
Hospital São Paulo,
Departamento de Neurologia e
Neurocirurgia,
Universidade Federal de São Paulo,
Rua Napoleão de Barros, 737, 13º andar,
CEP-04024-002 São Paulo-SP, Brazil
<taissaferrari@uol.com.br>

Rasmussen encephalitis (RE) is a rare progressive inflammatory disease characterised by refractory focal epilepsy, most commonly presenting as *epilepsia partialis continua* (EPC), followed by focal neurological and cognitive deterioration with neuroimaging evidence of unilateral

cerebral hemiatrophy (Bien *et al.*, 2007).

We report a case of a child with RE in whom the first clinical sign was progressive hemiparesis without epilepsy from age two and a half years, followed almost three years later by seizures presenting as

periodic epileptic spasms. Pathological studies performed after surgical treatment also revealed, along with the anticipated signs of inflammation, features of focal cortical dysplasia (FCD).

Case study

A five-and-a-half-year-old girl started experiencing progressive left hemiparesis at age two and a half years. There was no previous medical history. Aside from hemiparesis, she had normal development until the age of four, when she ceased to gain new cognitive skills. At age five years and four months, she started presenting clusters of asymmetric epileptic spasms, lasting up to ten minutes, occurring twice daily during wakefulness, without any impairment of consciousness. Treatment with oxcarbazepine was ineffective. Neurological examination at the time of admission showed complete left hemiparesis, most marked in the face and hand, with no useful function or fine finger movement. Neuropsychological assessment disclosed a moderate impairment in all domains. Cerebrospinal fluid analysis was unremarkable.

A video-electroencephalographic study (V-EEG) revealed diffuse background slowing, more marked in the right hemisphere, and frequent sharp waves over the right frontotemporal region (*figure 1A*).

A total of five stereotyped clusters of spasms were recorded. At the onset of each cluster, the patient showed sudden asymmetric flexion of axial and proximal muscles, predominantly in the left arm, often associated with rictus-type facial grimaces (*see video sequence*). Each spasm, repeated every 5-13 seconds, lasted for 1-2 seconds, and each cluster lasted 9-12 minutes. Ictal EEG consisted of bursts of high voltage, generalised, symmetric, repetitive polyphasic complexes, formed by irregular slow waves superimposed by spikes, ranging from 0.5-2 seconds in duration, usually recurring every 5-13 seconds. EMG recording revealed a typical diamond-shape aspect, corresponding to progressive muscular contraction followed by progressive decontraction (*figure 1B*).

The aspect of periodic complexes was fairly constant and stereotyped in each EEG channel (*figure 1C*). Intensity and frequency of the spasms in each cluster did not increase in a *crescendo* fashion, peaking and then slowly decreasing in intensity, as usually seen in infantile spasms.

Head CT performed at the onset of symptoms showed localised atrophy of the right cerebral hemisphere. Three months later, brain MRI confirmed the atrophy and also revealed an increased T2 signal in the ipsilateral corona radiata and insula. Subsequent MRI performed three years later showed progression of the disease (*figure 2*).

With clinical, neurophysiological and neuroimaging data suggesting RE, the child underwent a right hemispherotomy with in-block resection of the insula.

Histological examination of the resected cortex showed inflammatory changes characterised by microglial nodules, focal chronic inflammatory cell aggregates, neuronophagia and lymphocytic perivascular cuffing (*figure 3C*). A chronic inflammatory leptomeningeal infiltrate was also present. In some areas, abnormalities of cortical organisation (*i.e.* disruption of the normal cortical laminar architecture) were also observed (*figure 3A*). There was mild focal neuronal loss. Heterotopic neurons in the deep cerebral white matter were noted, some of which were dysmorphic, characterising type IIa FCD (*figure 3B*).

The patient has been seizure-free for 16 months since surgery, on carbamazepine. She had a slight worsening of the left hemiparesis, and is able to walk without assistance.

Discussion

RE is a progressive inflammatory disease of unknown origin which occurs mainly in childhood, usually affecting one hemisphere of the brain, and is associated with well defined clinical, neuroimaging and pathological characteristics (Bien *et al.*, 2007).

The typical clinical disease course is divided into three stages: 1) a *prodromal period* characterised by a relatively low seizure frequency, and rarely some degree of hemiparesis (minor disease signs and symptoms); 2) an *acute stage* characterised by *epilepsia partialis continua* or other seizure types (simple and complex partial motor seizures or secondary generalised seizures), followed by development of progressive decline of functions associated with the affected hemisphere; and 3) a *residual stage*, when the patient has a stable neurological deficit and lower seizure frequency (Bien *et al.*, 2007).

The reported case is unique in three aspects: 1) typical RE features of progressive unilateral brain involvement were present without seizures; there was a delay of almost three years prior to seizure onset; 2) an atypical seizure type presentation was identified with periodic epileptic spasms; and 3) the presence of FCD associated with inflammatory changes was determined.

Diagnosis of RE without seizures may be overlooked in childhood. Delayed-onset seizures in RE have been previously described in patients with hemiparesis as the initial clinical manifestation, followed by seizures after a delay of up to one year and 11 months. In cases of progressive unilateral neurological deficits, RE must be considered. If serial MRI studies are suggestive of this diagnosis, brain biopsy is recommended, and in the presence of T-cell mediated encephalitis with

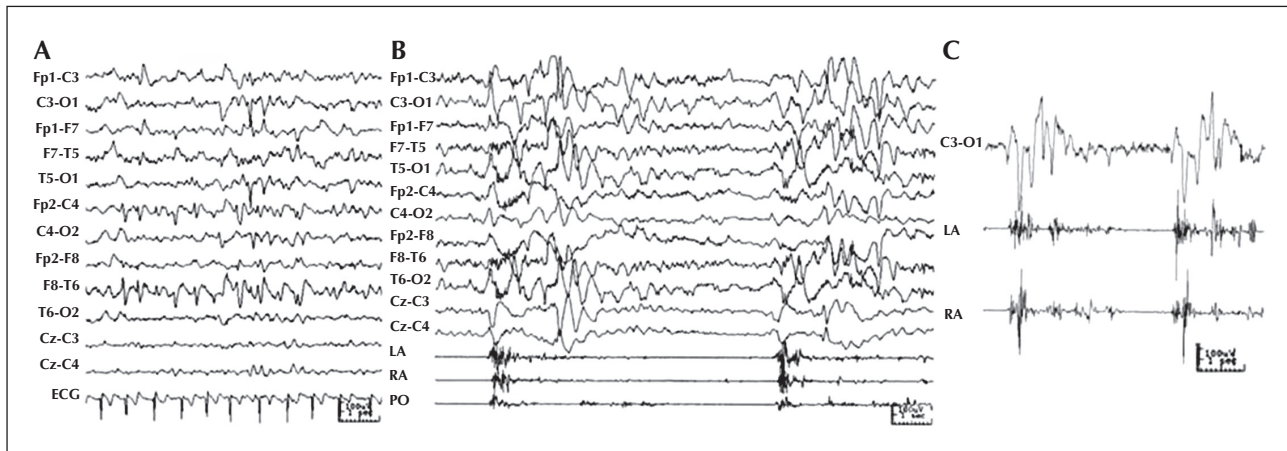


Figure 1. A) Interictal EEG with diffuse background slowing, more marked in the right hemisphere, and frequent sharp waves over the right frontotemporal region.

B) Ictal EEG with bursts of high voltage, generalised, symmetric, repetitive polyphasic complexes formed by irregular slow waves superimposed by spikes. EMG recording revealed a typical diamond-shape format.

C) The aspect of periodic complexes was fairly constant and stereotyped in each EEG channel.

LA: left arm; RA: right arm; PO: perioral.

microglial activation, RE can be safely diagnosed (Bien *et al.*, 2007).

To the best of our knowledge, RE with periodic epileptic spasms has not yet been described. The term “epileptic spasms”, which includes infantile spasms, has been previously recognised and consists of a series of motor movements, involving sudden flexion/extension predominantly of axial and/or proximal

limb muscles, occurring with a noticeable periodicity. Because spasms may continue, or even occur *de novo*, after infancy, the more general term “epileptic spasms” is used (Goldstein and Slomski, 2008). However, current knowledge is considered inadequate to make a firm decision regarding whether spasms should be classified as focal, generalised, or both. Therefore, in the new revised terminology and

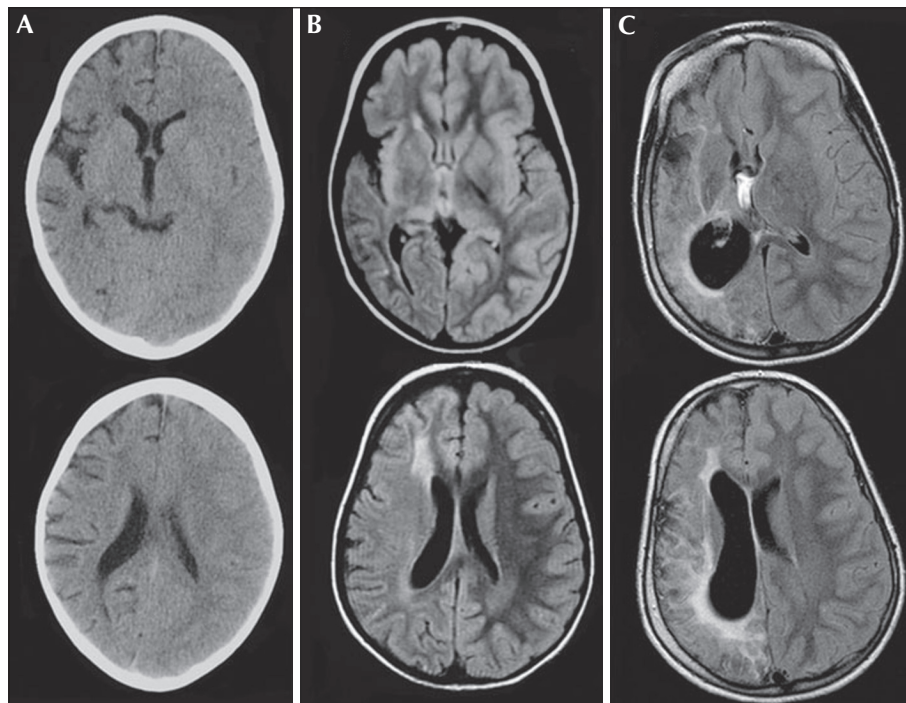


Figure 2. A) CT performed at the onset of symptoms (two and a half years.) with localised atrophy of the right cerebral hemisphere.

B) MRI at two years and eight months with hemiatrophy and increased T2 signal in the ipsilateral corona radiata and insula.

C) MRI performed at five years and eight months with severe right brain hemiatrophy involving cortical and subcortical structures.

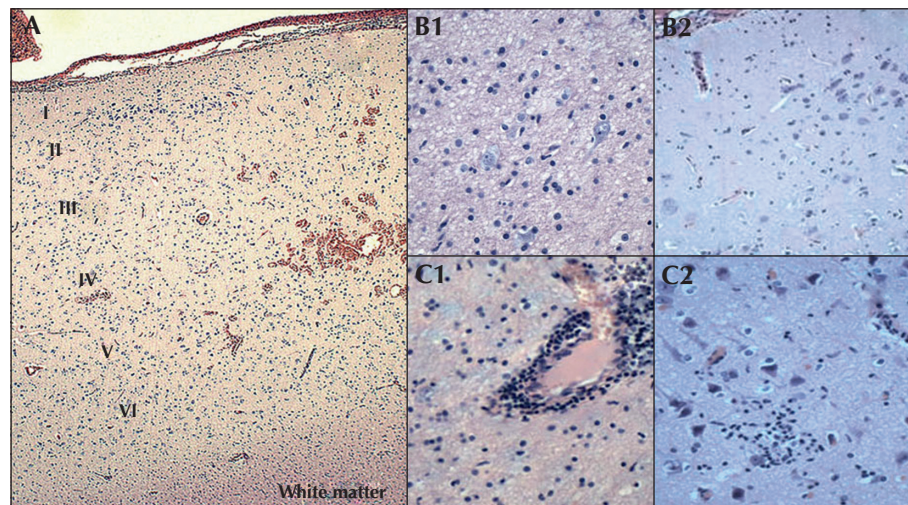


Figure 3. Histology of the resected specimen.

A) Delaminated cerebral cortex and overlying leptomeninges with mononuclear inflammatory infiltrate and haemorrhage (haematoxylin and eosin [HE], original magnification 40x).

B) Dysmorphic features; dysmorphic neurons in the neocortex white matter (HE, original magnification 200x) (**B1**) and delaminated cerebral cortex (HE, original magnification 100x) (**B2**).

C) Inflammatory features; perivascular lymphocytic infiltration of the cerebral cortex (HE, original magnification 200x) (**C1**) and cerebral cortex with microglial nodules (HE, original magnification 200x) (**C2**).

concepts for organisation of seizures and epilepsies by the ILAE, they have been placed in their own group as “unknown” (Berg *et al.*, 2010).

The term “periodic spasm” was first proposed by Gobbi *et al.* (1987) for epileptic spasms that occur at different ages in patients with localisation-related epilepsy. Periodic spasms constitute an unusual form of epileptic seizure, usually resistant to treatment, and up to now, only found in patients with brain disorders and more frequently fixed or metabolic encephalopathies (Gobbi *et al.*, 1987). As in the case we report, the authors mentioned periodic spasms in clusters without hypsarrhythmia, but interictal EEG with focal epileptiform discharges and ictal pattern characterised by slow-wave complexes. These complex graphoelements are similar to those seen in subacute sclerosing panencephalitis and were similarly stereotyped in each channel and periodic (*figure 1C*). The pathophysiological mechanism of periodic EEG discharges is still unknown. It has been suggested that periodicity results from a diffuse or local alteration in neuronal excitability responsiveness to input from distant areas and that this alteration may have a biochemical or anatomical basis (Brenner and Schaul, 1990).

Since Gobbi *et al.* (1987), others have reported the occurrence of spasms after the first year of life (Bednarek *et al.*, 1998; Auvin *et al.*, 2010). Late-onset spasms (LOS) are considered as epileptic spasms with typical electroclinical features associated with a specific age-related epileptic encephalopathy. Whether LOS should be considered as a separate epileptic syndrome, as an intermediate between West and

Lennox-Gastaut syndrome (LGS), is an issue that has been discussed (Auvin *et al.*, 2010; Eisermann *et al.*, 2006). The occurrence of periodic late-onset spasms starting in a child of five years and four months old with progressive hemisphere atrophy was an unexpected finding. Recognition of this entity is important to prevent delayed diagnosis and to improve early choices of appropriate treatment (Bednarek *et al.*, 1998; Auvin *et al.*, 2010).

There is, at present, no conclusive evidence as to why and how RE begins. Available data suggest an immune basis to the pathogenesis of RE. Pathophysiology remains elusive and a vicious circle linking inflammation and epilepsy has been suggested; inflammation and cell necrosis could lead to an epileptic encephalopathy, which could in turn enhance blood-brain barrier opening and cell necrosis, eventually promoting seizure activity. It has been debated whether the inflammation causes epilepsy or the epileptic activity leads to inflammation resulting in brain parenchymal damage. It has been suggested that in RE, the epileptic activity itself may contribute to the functional decline (Gataullina and Dulac, 2010). Nevertheless, this case demonstrates that the manifestation of epilepsy can be dissociated timely from the inflammatory and degenerative features of RE, confirming that RE can occur without seizures or with delayed-onset seizures, and is otherwise indistinguishable from RE cases with seizures from the onset (Bien *et al.*, 2007). The absence of seizures in the presence of brain inflammation raises an important issue, lying at the basis of the understanding of the pathogenesis of RE.

Since brain involvement is mainly unilateral in RE, some additional factor must contribute to the pathogenesis in order to determine unilaterality (Bien *et al.*, 2007). There are reports linking infection or cerebral malformations to RE. The coexistence of a neuronal migration defect with inflammatory changes in RE (dual pathology) has previously been reported, however the prevalence is discrepant in the literature, ranging from less than 10% to 100% of cases of RE (Hart *et al.*, 1998; Takei *et al.*, 2010). It is argued that dysplastic changes in RE might have been overlooked in reported cases due to the more evident histological changes associated with RE (Takei *et al.*, 2010). The co-occurrence of the malformative and inflammatory lesions raises questions about a possible causal relationship between these two entities (Takei *et al.*, 2010). In conclusion, the clinical picture of RE may have a protracted course with late focal periodic epileptic spasms. Association with FCD raises a new hypothesis for the physiopathology. □

Disclosure.

None of the authors has any conflict of interest or financial support to disclose.

Legend for video sequence

The patient presenting with periodic spasms characterised by sudden asymmetric flexion of axial and proximal muscles, predominantly in the left arm, often associated with rictus-type facial grimaces. She answers questions without any impairment of consciousness.

Key words for video research on www.epilepticdisorders.com

Etiology: Rasmussen encephalitis

Phenomenology: spasm (epileptic), motor seizure (complex)

Localization: hemispheric, insula (right)

Syndrome: Rasmussen syndrome

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