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Presentation, diagnosis and treatment of bilateral Rasmussen's encephalitis in a 12-year-old female

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ABSTRACT – *Aim.* To describe the clinical course and pathological diagnosis of a 12-year-old female who presented with an acute syndrome of right hemispheric epilepsy and cortical dysfunction and brain MRI demonstrating atrophy of the left cerebral and right cerebellar hemispheres. *Results.* The patient presented with occasional partial seizures consisting of a left calf sensation followed by left leg clonic jerking. Initial brain MRI showed left cerebral and right cerebellar atrophy with T2 hyperintensity in the left parietal region. After six months, the seizure frequency increased and semiology evolved to include frequent clonic movements of the left side of the face, arm and leg and epilepsia partialis continua (EPC) of the left arm and leg. There was progressive weakness of the left leg and, to a lesser extent, her left arm. MRI at this time demonstrated an additional T2 hyperintensity in the right frontal lobe. An extensive evaluation for paraneoplastic, mitochondrial, and genetic epilepsy syndromes was unrevealing. On biopsy evaluation, chronic T-cell mediated encephalitis was demonstrated within bilateral frontal lobes. Treatment with immunomodulatory therapy resulted in some improvement in her seizure frequency and motor function. *Conclusion.* Rasmussen's encephalitis can be a challenging diagnosis. The patient's clinical history, including EPC, with bilateral frontal lobe biopsies confirming a T-cell mediated encephalitis supports a diagnosis of bilateral Rasmussen encephalitis. This case highlights the diagnostic challenges and treatment dilemmas that arise in an adolescent presenting with bilateral inflammatory lesions of Rasmussen's encephalitis. [*Published with video sequences*]

Key words: bilateral Rasmussen, chronic encephalitis, Rasmussen syndrome, Rasmussen's encephalitis

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Rasmussen's encephalitis (RE) is a syndrome of chronic localised encephalitis involving a single cerebral hemisphere, treatment of refractory epilepsy, and neurological impairment (Rasmussen *et al*., 1958). The aetiology of RE remains unknown. Neuropathological studies demonstrating neuroglial and lymphocytic responses consistent with other autoimmune CNS diseases (Pardo *et al*., 2004) and case reports demonstrating efficacy of rituximab therapy (Thilo *et al*., 2009) point to an autoimmune origin. Three clinical stages (prodromal, active, and residual) have been described and the syndrome is diagnosed based on published clinical criteria (Bien *et al*., 2005). However, atypical cases have been reported, including adolescent/adult onset, delayed epilepsy onset, absence of epilepsy, and extremely rare cases of bilateral RE (Andermann and Farrell, 2006; Bien *et al*., 2007; Ramesha *et al*., 2009; Guan *et al*., 2011). There have been a dozen reported cases of bilateral RE, but given the lack of biopsy/autopsy confirmation of bilateral involvement in the majority of cases, it is difficult to be certain of the diagnoses in all cases. Herein, we describe a case of biopsy-confirmed bilateral RE.

Case study

The patient was a 12-year-old, left-handed female who presented with new-onset seizures consisting of a painful left calf sensation that progressed to the contralateral leg and left arm with face numbness, followed by a "figure of four" sign related to tonic left arm extension and a bent right arm. The seizures lasted less than two minutes, and afterwards, she would have a left mouth droop and slurred speech for 20-30 minutes. Her neurological examination at presentation demonstrated right upper extremity dysmetria and intention tremor. Treatment with levetiracetam was initiated, but she continued to have intermittent breakthrough seizures. Her initial 24-hour EEG study was normal. Head CT and brain MRI obtained near the onset of her epilepsy showed marked volume loss and abnormal T2 signal in the left cerebral parenchyma, in addition to volume loss in the right cerebellum (*figure 1B, C*). Head CT had been obtained nearly five years prior to symptom onset after a minor head trauma (*figure 1A*), which showed milder right cerebellar volume loss, but no evidence of left hemispheric abnormality. Thus, the imaging findings at the onset of her epilepsy were consistent with interval left hemispheric volume loss and presumed cerebellar diaschisis.

The frequency and semiology of her seizures evolved over time. She was admitted six months after seizure onset for multiple daily seizures with interictal disinhibition, mood lability, and memory problems. The EEG performed during this hospitalisation captured multiple seizures, demonstrating right hemispheric onset in Pz-P4 (*figure 2*). Given her clinical presentation, a diagnosis of RE was considered in addition to infectious causes of encephalitis, progressive myoclonic epilepsy, mitochondrial epileptic encephalopathy, and an autoimmune-mediated epilepsy (*table 1*).

The patient's seizure frequency continued to increase, with a slightly more anterior localisation on EEG (*figure 2*). She developed a left hemiparesis, most severe in her distal left leg. Review of serial brain MRI over an eight-month period after seizure onset demonstrated increasing T2 hyperintensity in the left frontal and anterior parietal lobe and new increased T2 signal in the medial right frontal lobe (*figure 1C, D, F*). The left cerebral hemisphere and right cerebellar hemisphere volume loss remained stable. ^{18}FDG PET showed intense glucose uptake in the parasagittal region of the right posterior frontal lobe near the central sulcus in the area of the new MRI signal, with otherwise extensive areas of decreased metabolism in most of the left frontal lobe, right cerebellar hemisphere, and the superior aspect of both parietal lobes (*figure 1E*). Interictal and ictal MEG source localisation supported a right parasagittal focus. With no obvious underlying aetiology and evolving clinical history, RE was the primary diagnostic consideration, however, the bilateral imaging findings complicated the diagnostic picture.

The patient's left leg and arm focal motor seizures evolved into EPC, in spite of therapeutic doses of multiple antiepileptic drugs (phenytoin, levetiracetam, oxcarbazepine, clonazepam, lacosamide, valproic acid, zonisamide, diazepam, vigabatrin, and phenobarbital), IVIg, and a four-week course of rituximab. A bicoronal craniotomy was performed and biopsies were taken from the parasagittal region of bilateral frontal premotor areas to aid in the diagnosis. Biopsy samples from both frontal cortices and white matter were consistent with a T-cell mediated encephalitis (*figure 3*). It was noted that the patient had been treated with rituximab, which effectively depletes CD20+ B cells, possibly altering some aspects of the biopsy sample. A neuropathological expert second opinion confirmed the diagnosis as most consistent with RE. With the patient's EPC and biopsy-confirmed chronic inflammatory changes, the criteria proposed by Bien and coworkers (Bien *et al*., 2005) for right hemispheric RE were met. Since the pathological process was clearly present in both hemispheres, she was diagnosed with bilateral RE.

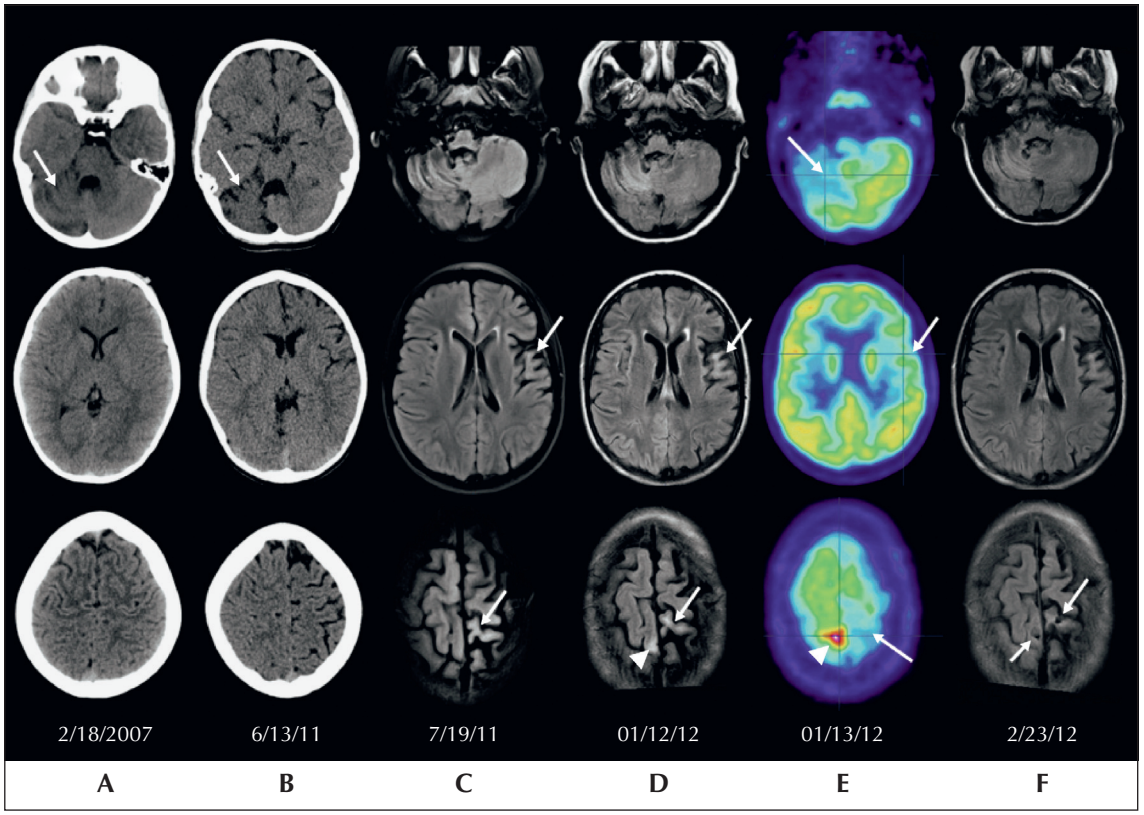

Figure 1. A) Initial CT scan obtained in 2007 (over four years prior to seizure onset). Note moderate right cerebellar volume loss (arrow). No other abnormality was identified. There was no evidence of left hemispheric volume loss. B) Head CT obtained at seizure onset in June 2011 demonstrated right cerebellar volume loss, which progressed slightly relative to the previous CT examination (arrow). Volume loss in the left cerebral hemisphere was identified, predominantly involving the frontal and anterior parietal lobe near the vertex. C) MRI obtained one month later (axial T2 FLAIR) demonstrated left hemispheric volume loss, right cerebellar volume loss, and increased signal consistent with gliosis (arrowhead), and regions of increased signal in the left hemispheric cortex and subjacent white matter (arrows). The right cerebral hemisphere was normal. D) MRI obtained with worsening daily seizures involving the left arm and leg (axial T2 FLAIR). New signal abnormality was noted in the right posterior frontal lobe involving the medial precentral gyrus and paracentral lobule (arrowhead). Persistent signal abnormalities were noted in the left hemisphere (arrows). Right cerebellum volume loss and signal were stable. E) FDG-PET performed the next day, with continued seizures, demonstrated a region of localised hypermetabolism (arrowhead) in the right posterior medial frontal lobe corresponding to the signal abnormality in (D). Regions of moderate to marked hypometabolism were noted in the left hemisphere and right cerebellum (arrows). F) MRI obtained after bilateral frontal biopsies, plasmapheresis, rituximab, and steroids (axial T2 FLAIR). Biopsy sites were identified in areas of previously noted signal abnormalities in the posterior frontal lobes at the vertex (arrows). Signal abnormality on the right decreased. Other areas of left hemispheric signal and right cerebellar volume loss were stable.

Post-biopsy, trials of intravenous solumedrol, rituximab, and plasmapheresis did not provide meaningful improvement in the patient's symptoms. She was initiated on monthly intravenous immunoglobulin (IVIG) infusions. Functional MRI evaluation demonstrated left language lateralisation. The option of a right functional hemispherotomy to treat her EPC was discussed with the patient and her family. However, they were reticent to incur the expected neurological deficits associated with this procedure in the context of an uncertain prognosis for her left hemisphere, given that the biopsy demonstrated bilateral inflammation. They declined surgery at this time. Her seizure frequency has remained stable to mildly improved six months post biopsy, with parents reporting 6-15 seizures per day. She continues to have moderate left hemiparesis but is ambulatory and has use of her left hand, with stable cognitive function.

Discussion

This report describes the diagnostic challenges and treatment dilemmas that arise in a pathology-confirmed case of bilateral RE. Of the more than 200 reported cases of RE in over 50 years, there are

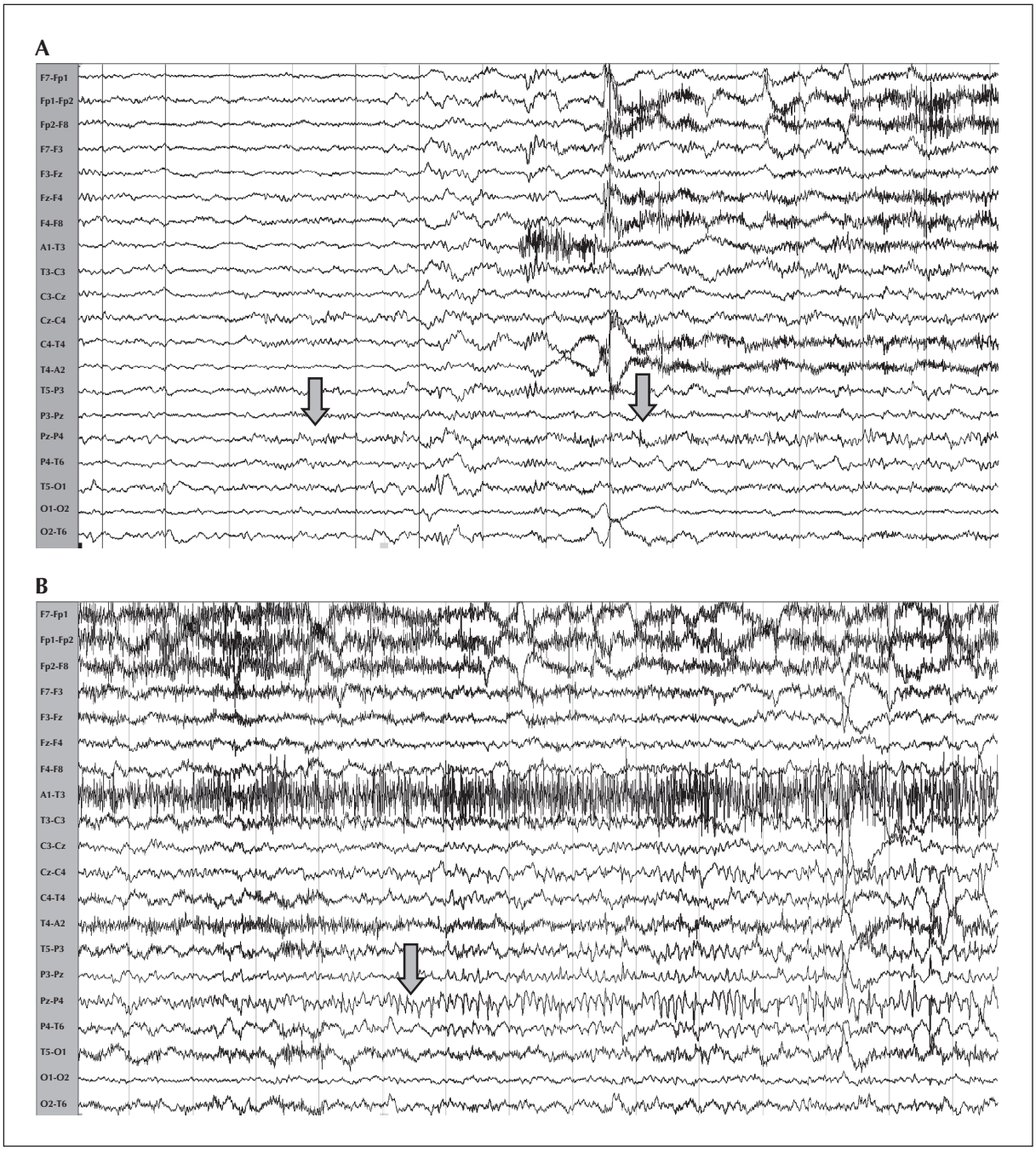

Figure 2. Representative EEGs from December 2011 (A and B: seizure+45 seconds; transverse montage) and January 2012 (C: average montage, see next page) showing evolution of the patient's seizures from focal onset at Pz-P4 to EPC centred over Pz.

less than 12 cases that meet the criteria for diagnosis of bilateral RE (Bien *et al*., 2005) (*table 2*), and only two have pathology-verified bilateral disease, performed at autopsy. This patient meets the two B-criteria described by Bien *et al*. (2005) for diagnosis of RE, namely *epilepsia partialis continua* and biopsy-confirmed T cell-dominated encephalitis with activated microglia and reactive astrogliosis. The patient presented with a right hemispheric syndrome of explosive right parasagittal seizures, interictal cortical dysfunction resulting in left hemiparesis, and EEG/MEG findings consistent with right parasagittal

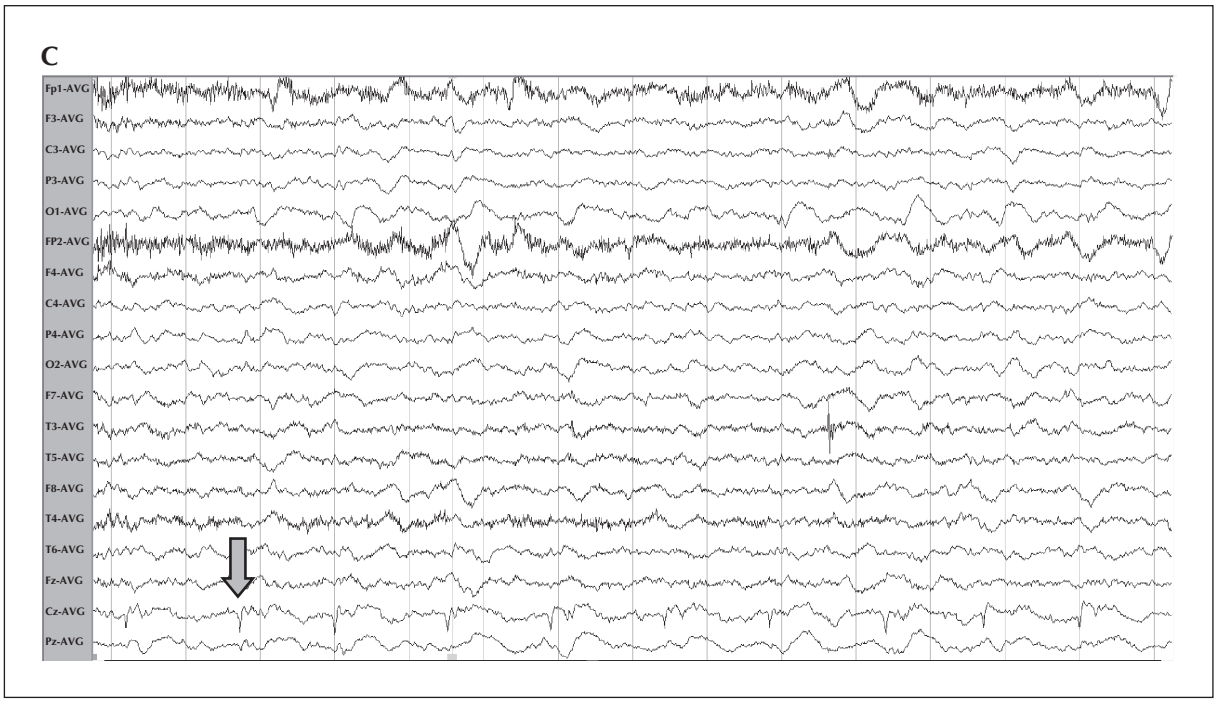

Figure 2. (*Continued*): January 2012 EEG showing evolution (C: average montage).

localisation. The patient did not demonstrate significant right hemispheric cerebral volume loss during the course of her illness, but it was unclear how much the aggressive immunomodulatory therapy she received would alter this finding. The pathology confirmed that the inflammation was clearly bilateral.

This case report has some limitations. Although an extensive workup to investigate causes of encephalitis was performed, an undiagnosed aetiology cannot be ruled out. Second, to preserve function, restricted biopsies were obtained from both hemispheres, limiting the ability to diagnose a potential dual pathology, such as focal cortical dysplasia, that may have been possible with a larger resection. Third, although both hemispheres demonstrated similar pathology, the patient had no clear neurological symptoms from the progressive atrophy of the left cerebral hemisphere. This contrasts with previously reported cases of bilateral RE showing bilateral neurological signs (Chinchilla *et al*., 1994; Takahashi *et al*., 1997; Silver *et al*., 1998; Tobias *et al*., 2003; Guan *et al*., 2011). Nonetheless, there are reports of atypical cases of RE that have demonstrated diffuse hemiatrophy and functional impairment for 1.3-1.9 years prior to seizure onset in addition to cases without seizures (Bien *et al*., 2007).

The degree of hemiatrophy in the left cerebral hemisphere with crossed cerebellar diaschisis and minimal associated neurological dysfunction on initial examination is an unusual feature of this case. It seems unlikely that the patient would have had a chronic encephalitis involving the left cerebral hemisphere leading to crossed cerebellar diaschisis while remaining asymptomatic from a neurological and developmental perspective. In addition, the right cerebellar atrophy was noted prior to symptom onset, before the left hemisphere atrophy observed at epilepsy onset (*figure 1A, B*). Cianfoni *et al*. (2010) reported the presence of crossed cerebellar diaschisis on brain MRI at five years of follow-up in a patient with biopsy-confirmed RE. However, the timing of symptom onset with the corresponding imaging findings in this report does not correlate with that seen in our patient. The patient in our report was symptomatic for only one month before the left cerebral atrophy was first identified on MRI. Her parents reported a left-handed preference since 3 years of age, suggesting the left cerebral hemisphere volume loss and the crossed cerebellar diaschisis may be secondary to a remote injury, causing a pathological left-handedness. Cerebellar atrophy prior to hemispheric atrophy has been described after neonatal cerebellar injuries (Limperpoulos *et al*., 2005) in addition to cerebellar strokes in adults, although obvious areas of cerebellar injury were absent in imaging studies of this patient (*figure 1A-C*). Apparent evolu-

Table 1. Summary of the laboratory diagnostic work-up.

Test	Results (where given)	Interpretation
Serum Amino Acids	Elevated Alanine	Likely secondary to seizure activity
Lactate Pyruvate	1.60 mmol/L 0.12 mmol/L	Normal
Carnitine	Total: 43.4 nmol/mL Free: 33.1 nmol/mL Short: 10.3 nmol/mL	Normal
Acylcarnitine profile	Normal free carnitine Several longer chains Elevated 2 fold	Fasting pattern
Ammonia	21 μmol/L	Normal
Urine organic acids	Lactate elevated 2 fold	No diagnostic pattern
Urine metabolic screen		Normal
TSH/Free T4/anti-TPO Ab	TSH: 1.07 mIU/mL FT4: 1.4 ng/dL Anti-TPO Ab: <5 IU/mL	Normal
ESR	5 mm/hr	Normal
CRP	<0.3 mg/dL	Normal
ANA		Negative
Serum Lyme IgM/IgG		Negative
Serum mycoplasma IgM/IgG		Negative
Serum arboviral panel		Negative
POLG1	No known deleterious mutations	Negative
Progressive Myoclonic Epilepsy Panel (EPM1/2A/2B, Lafora, MERRF, EFHC1)	No variants or mutations found	Negative
Muscle biopsy/ETC studies	No inclusions, RRF No ETC abnormalities	Normal
CSF cell counts (WBC/RBC)	0/71	Normal
CSF glucose	59 mg/dL	Normal
CSF protein	39 mg/dL	Normal
CSF cultures and gram stain	No organisms; No growth	Normal
CSF OCB	7	Positive
CSF IgG	2.6 mg/dL	Normal
CSF Amino Acids	Thr, Glu Elevated	Non-diagnostic pattern
CSF lactate/pyruvate		Normal
CSF anti-NMDA		Negative
CSF paraneoplastic antibody panel*		Negative
CSF Arbovirus		Negative
CSF VZV		Negative
CSF HHV6		Negative
CSF HSV 1/2		Negative
CSF EBV		Negative
CSF CMV		Negative
CSF Enterovirus		Negative
CSF Influenza A/B		Negative

*Paraneoplastic antibody panel + Anti-NMDA Ab Mayo Clinic included antibodies against: NMDA, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, CRMP-5-IgG, PQ-type calcium channel, N-type calcium channel, ACh receptor, AChR ganglionic neuronal, neuronal (V-G) potassium channel, and striational Abs.

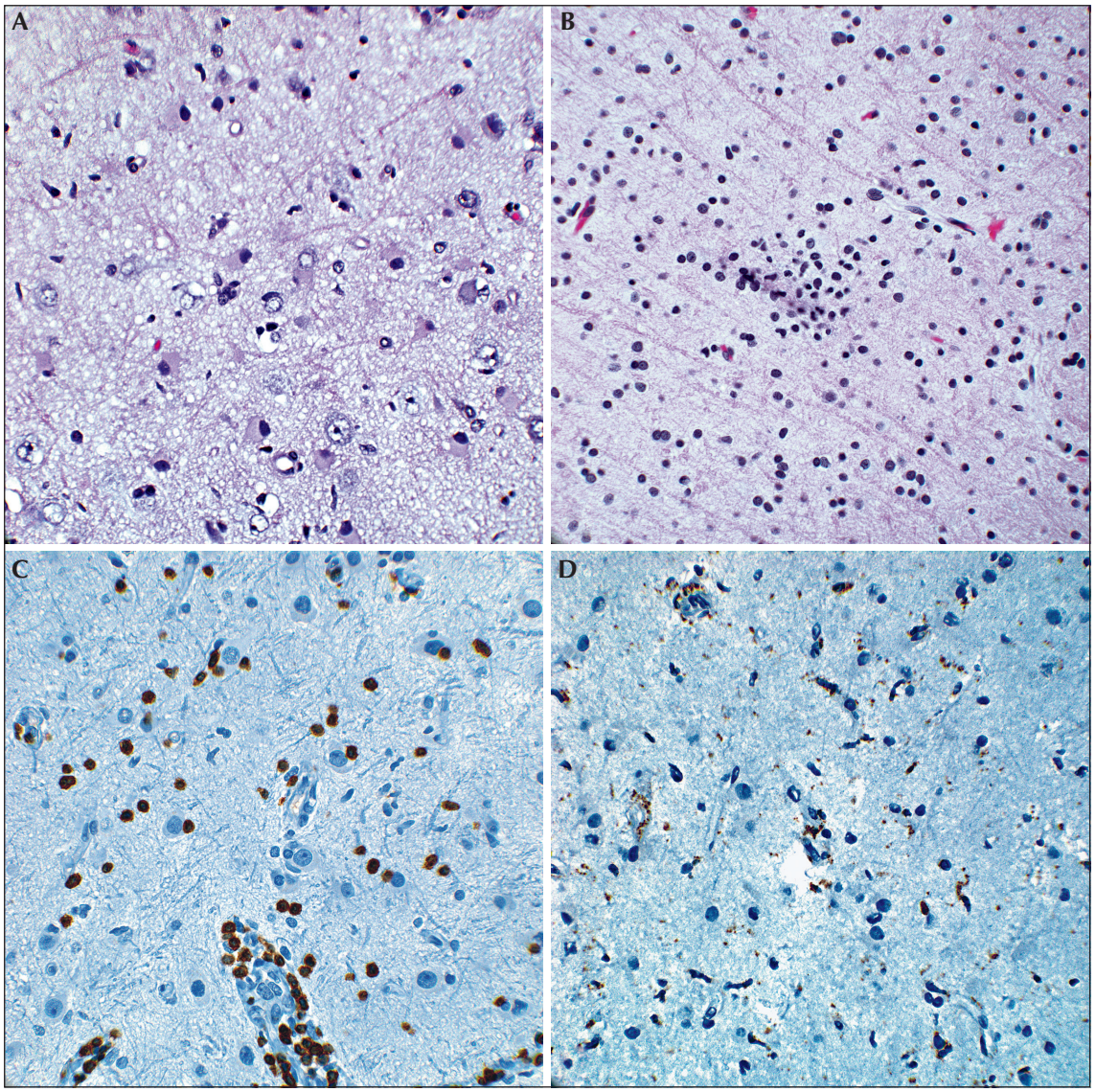

Figure 3. Bilateral brain biopsies demonstrated dural fibrosis without inflammation. Similar changes were observed in right and left frontal grey and white matter. Gliosis was evident with the presence of gemistocytic astrocytes (A) and inflammatory infiltration, composed of CD3 positive T-lymphocytes (C) and CD68 positive microglia (D). The inflammatory cells were seen scattered in the parenchyma and around blood vessels. CD20 positive B-lymphocytes were not identified. A microglial nodule was seen in the left frontal white matter (B). A few red neurons and neurons with chromatolysis were present. No dysmorphic or balloon cells were identified.

tion of left cerebral atrophy over four years argues against a completely static left hemispheric process. Various causes of primary pathology with secondary activation of inflammation, so-called "*dual pathology*" in RE, have been well-described (Silver *et al.*, 1998). In this case report, dual pathology of our patient's left cerebral and right cerebellar atrophy can only be speculated.

The recommended treatment for seizure control in RE, based on expert opinion, is hemispherotomy. Immune modulatory therapy is a secondary treatment, mostly to help prevent the neurological decline observed in these patients. This treatment protocol is generally followed in patients with very early onset of disease and those in which the seizures are the most prominent morbidity in the illness. There is no such consensus for patients with bilateral disease. The treatment of our patient falls into a category described by Bien and Schramm (2009) as a therapeutic dilemma. This patient had a later clinical onset of disease suggesting less risk of mortality. Her acute syndrome was right hemisphere in origin, but she had clear bilateral

Table 2. Reported cases of bilateral Rasmussen's encephalitis.

Reference	Age at first seizure	Focal deficits	EPC	Hemispheric atrophy MRI/CT	Pathology confirmation
Guan *et al*., 2011	2 years	bilateral	+ bilateral	+	+ Left fronto-parietal; No pathology from right hemisphere
Chinchilla *et al*., 1994	5.9 years	bilateral	+ bilateral	+	None
Chinchilla *et al*., 1994	3.5 years	unilateral	+ bilateral	+	+ single occipital lobe
Chinchilla *et al*., 1994	8.75 years	unilateral	+ bilateral	+	+ bilateral (necropsy)
Tobias *et al*., 2003	2.5 years	bilateral	No	+ (bilateral)	+ bilateral (necropsy)
Farrell *et al*., 2002	2.75 years	NR	+ right	+	+ right hippocampus
Silver *et al*., 1998	0.5 year	bilateral (L>R)	+ bilateral	-	+ right frontal
Silver *et al*., 1998	0.3 year	bilateral	+ bilateral	+ (bilateral)	None
Takahashi *et al*., 1997	0.17 years	bilateral	+ bilateral	+ (bilateral)	None
Takahashi *et al*., 1997	0.17 years	bilateral	+ bilateral	+ (bilateral)	None
Takahashi *et al*., 1997	2.4 years	bilateral	+ bilateral	+ (bilateral - left before right)	None
DeToledo and Smith, 1994	14 years	unilateral	+ unilateral	NR	+ left frontal lobe
DeToledo and Smith, 1994	11 years	unilateral	+ unilateral	+	+ bilateral

cortical and white matter inflammatory changes on pathology. Post-hemispherotomy, she would be reliant on a compromised hemisphere leading to an uncertain prognosis. Bilateral RE treatment decisions should be approached on an individual basis, but aggressive immune therapy is a valid alternative to surgery. □

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Legends for videosequences

Representative seizure shown in the electroencephalograms of *figure 2A, B*, prior to development of left upper and lower limb *epilepsia partialis continua*.

Key words for video research on www.epilepticdisorders.com

Syndrome: Rasmussen syndrome
Etiology: encephalitis
Phenomenology: clonic seizure; tonic posture
Localization: central (right)

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