



Case Report

Rasmussen's encephalitis presenting as focal cortical dysplasia



D.J. O'Rourke^{a,*}, A. Bergin^a, A. Rotenberg^a, J. Peters^a, M. Gorman^a, A. Poduri^a, J. Cryan^c, H. Lidov^c, J. Madsen^b, C. Harini^a

^a Dept. of Neurology, Boston Children's Hospital, USA

^b Dept. of Neurosurgery, Boston Children's Hospital, USA

^c Dept. of Neuropathology, Boston Children's Hospital, USA

ARTICLE INFO

Available online 12 March 2014

Keywords:

Rasmussen's encephalitis
Focal cortical dysplasia

ABSTRACT

Rasmussen's encephalitis is a rare syndrome characterized by intractable seizures, often associated with epilepsy partialis continua and symptoms of progressive hemispheric dysfunction. Seizures are usually the hallmark of presentation, but antiepileptic drug treatment fails in most patients and is ineffective against epilepsy partialis continua, which often requires surgical intervention. Co-occurrence of focal cortical dysplasia has only rarely been described and may have implications regarding pathophysiology and management. We describe a rare case of dual pathology of Rasmussen's encephalitis presenting as a focal cortical dysplasia (FCD) and discuss the literature on this topic.

© 2014 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

1. Introduction

Rasmussen's encephalitis (RE) is a rare but severe immune-mediated brain disorder leading to unilateral hemispheric atrophy, associated progressive neurological dysfunction with intellectual decline, and intractable seizures [1–4]. It is a well-established cause of pharmacologically intractable epilepsy. Antiepileptic drug treatment fails in most patients and is ineffective against epilepsy partialis continua (EPC), which often requires surgical intervention [4]. Given the presence of autoantibodies in many cases, particularly GluR3 autoantibodies, a variety of immunotherapy treatments have been attempted with varied success [5–7].

Pathological features resemble a viral encephalitis. A viral cause of RE was suggested by Rasmussen et al. in 1958 [8]; however, reliable identification of an offending infectious agent has not been successful. Proposed etiologies have included defects in the humoral and innate immune systems. Microscopic analysis usually reveals inflammatory hallmarks of the disease, consisting of widespread perivascular T-cell infiltration and microglial nodule formation with neuronal cell death and cortical atrophy characteristic of advanced disease stage [4,9].

Co-occurrence of the destructive pathology of RE with dysplastic features in cortical architecture has only rarely been described but may have implications regarding pathophysiology and management [10–15]. Indeed, the role of other principal brain lesions in RE remains

controversial [16]. Therefore, we describe a rare case of dual pathology of RE presenting as a focal cortical dysplasia (FCD) and discuss the literature on this topic.

2. Case report

A previously healthy, 10-year-old right-handed girl with prior normal development presented at 8.5 years with twitching of the right side of her body initially involving the face and, later, arm, and leg. The twitching became essentially continuous during both wakefulness and sleep and evolved into epilepsy partialis continua (EPC). Electroencephalogram (EEG) showed frequent left-side spikes, but the initial MRI was normal and did not show any hemiatrophy.

One month postseizure onset, she developed recurrent fever, rash, lymphadenopathy, and mouth ulcers. She underwent an extensive infectious/inflammatory work-up which was significant for positive cerebral spinal fluid (CSF) oligoclonal bands. A lymph node biopsy was consistent with Kikuchi–Fujimoto disease, an idiopathic disorder characterized by fever and lymphadenopathy that may have an autoimmune basis and a possible association with systemic lupus erythematosus. However, investigations for lupus were unrevealing. The patient underwent immunotherapy involving steroids and immunoglobulin but without any clinical improvement.

The patient's EPC remained refractory to multiple anticonvulsant medications and a course of transcranial magnetic stimulation (TMS). She developed significant functional impairment initially affecting speech articulation and later developed an expressive aphasia with

* Corresponding author at: Dept. of Neurology, Division of Epilepsy, Fegan 9, Boston Children's Hospital, 300 Longwood, Boston, MA 02130, USA.

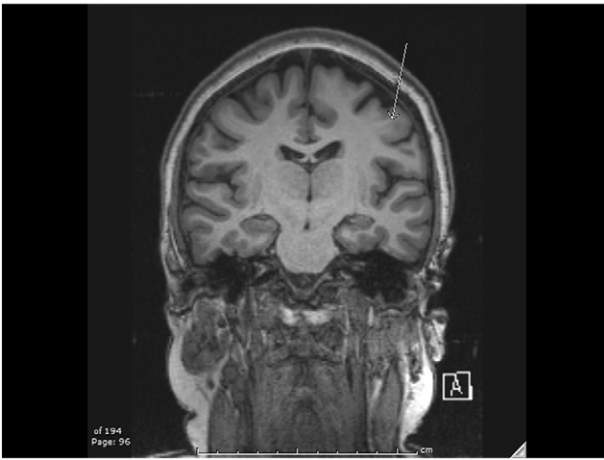


Fig. 1. Coronal T1 image showing blurring of the gray–white matter interface at the left precentral gyrus suspicious for focal cortical dysplasia.

impaired processing and comprehension. Follow-up neuropsychology evaluation showed cognitive decline. There was no hemiparesis.

Follow-up MRI 2 months postseizure onset demonstrated blurring of the gray–white junction in the left precentral gyrus and was concerning for a cortical dysplasia (Fig. 1). However, differential diagnosis still included a Rasmussen's encephalitis or a nonspecific autoimmune process. Given the persistent pharmacologically refractory focal seizures, the patient underwent a surgical evaluation. Electroencephalogram showed multiregional left hemispheric spikes and slowing. Positron emission tomography (FDG-PET) showed an area of hypometabolism in the left precentral gyrus, but there was no focal increased radiotracer uptake with ictal single-photon emission computed tomography. Magnetoencephalography showed a spike dipole cluster at the left precentral gyrus.

Motor mapping performed with TMS and functional MRI (fMRI) showed typical contralateral motor innervation but was directly related to the left precentral gyrus of concern. Language fMRI activation patterns recorded during passive language tasks were consistent with bilateral language activation in temporoparietal regions slightly favoring the left hemisphere and typical left-lateralized frontal lobe processing.

Given the concordant data for a left precentral lesion, the patient underwent invasive EEG monitoring to better localize the seizure onset zone. Grids and strips were placed over the left hemisphere convexity, and a wedge biopsy of the cortex was taken. This confirmed that the seizure onset zone overlapped the eloquent left hemisphere primary motor cortex for the contralateral hand, throat, and jaw and the left sensory cortex for the face.

Biopsy subsequently showed a mild to moderate T lymphocyte predominant inflammatory infiltrate in the cortex and white matter with microglial nodules, which was consistent with Rasmussen's encephalitis, but the overall pathological picture was mild (Figs. 2 and 3). In addition, rare dysplastic neurons were seen, suggesting a possible cortical dysplasia (Fig. 3d). Balloon cells were not identified. There was reactive gliosis, without vasculitis or viral inclusions.

In an attempt to avoid any deficits, the patient underwent a partial resection in the left frontal lobe, avoiding areas which mapped to hand motor function and language, and multiple subpial transections in the area of hand motor function were performed. Tissue taken during this surgery was similar to the one taken from the previous biopsy.

Following surgery, the patient started a monthly course of intravenous immunoglobulin (IVIG). At 3 months postop, her family felt that she had started to show some improvement, with her right hand becoming more functional and with decreased hand twitching, especially during sleep.

3. Discussion

Rasmussen's encephalitis is a rare syndrome characterized by intractable seizures, often associated with EPC and symptoms of progressive hemispheric dysfunction [1–4]. The typical features of RE are onset in childhood with a peak of incidence at the age of 6 years [3] and development of slowly progressive, neurological deterioration including hemiparesis, cognitive impairment, aphasia when the dominant hemisphere is involved, and imaging evidence of progressive, usually unilateral, cerebral atrophy. Seizures are the most common initial symptom.

The pathogenesis of RE is still largely unclear. A causative pathogenic viral agent has so far not been identified. Evidence supporting GluR3 autoantibody-induced injury is conflicting, and there are cases in which such autoantibodies do not appear to exist [4]. Rasmussen's encephalitis is now believed to be an ongoing and progressive immune-mediated process which induces apoptotic neuronal cell death and involves the neuroglial and lymphocytic response, leading to progressive deterioration of a single hemisphere [4,9]. These findings suggested a potential benefit of antiinflammatory and immunosuppressive therapy in patients with RE in order to attenuate seizures as well as progressive neurological deficits. Indeed, antiepileptic drug treatment fails in most patients and is ineffective against EPC. On the other hand, immunomodulation, plasmapheresis, and antiviral treatment approaches were reported to be beneficial to only a limited extent, slowing cognitive decline but having no effect on established EPC [5–7,17]. Indeed, our case had significant evidence for immune activation with oligoclonal bands present in the CSF and lymph node biopsy showing features of Kikuchi–Fujimoto disease, justifying immunotherapy in this patient prior to establishing the diagnosis of RE.

Dual pathology may be noted in 10% of patients and varies from low-grade tumor, cortical dysplasia, tuberous sclerosis, mesial temporal sclerosis, vascular abnormalities, or old ischemic lesions [16]. The earliest MRI changes include firstly cortical swelling, with a hyperintense T2/FLAIR signal (Stage 1). Later, normal volume and hyperintense signal were seen (Stage 2), followed by atrophy and hyperintense signal (Stage 3) and then progressive atrophy with normal signal (Stage 4) [2]. Atrophy and signal change are most prominent in the perisylvian region. In addition, other findings include atrophy of the ipsilateral head of the caudate nucleus in the majority of cases [18,19]. True bilateral RE is rare [20,21]. In our case, the persistent MRI finding of blurring of the gray–white junction in the left precentral gyrus was concerning for a cortical dysplasia. This was in the absence of other neuroimaging changes typical for RE. In addition, FDG-PET showed an area of hypometabolism in the left precentral gyrus, giving further evidence towards a focal lesion in our case.

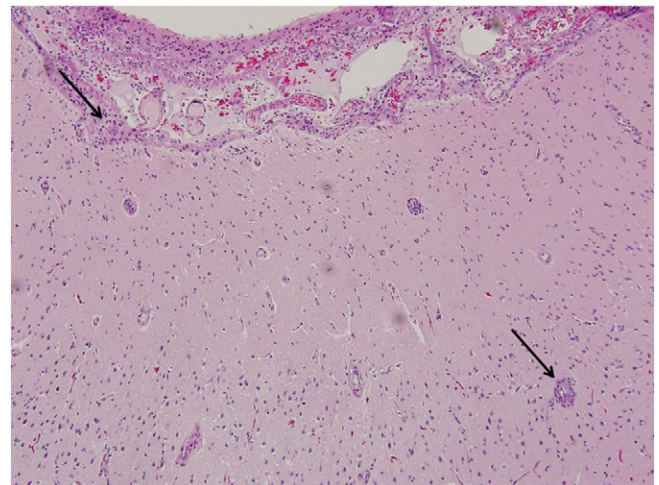


Fig. 2. Leptomeningeal and cortical lymphocytes.

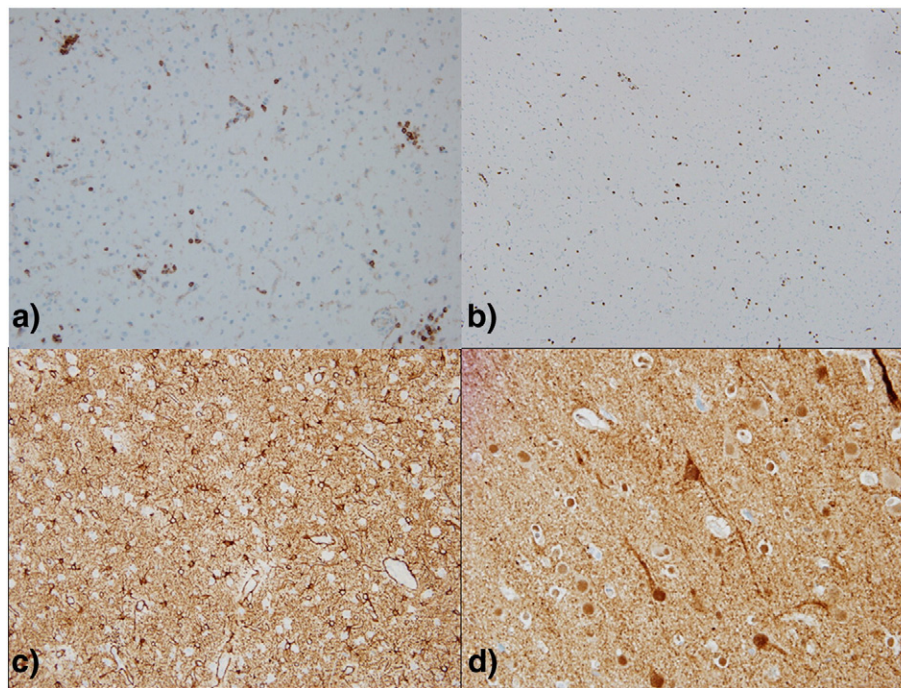


Fig. 3. a. CD45: lymphocytes, slightly more numerous than those seen on H&E. b. CD3: virtually all T-cells (no B-cells). c. GFAP: reactive gliosis. d. Rare SMI31 positive neurons of unclear significance.

All cases of RE and FCD involve children with a seizure onset in the first decade of life [10–15]. In all cases, the perioperative imaging studies did not reveal dual pathology, although FCD was considered in some. This current report is different in that a lesion concerning for FCD was identified on neuroimaging, but there was no evidence of RE. Instead, the combined clinical picture of EPC along with a T-cell-dominated encephalitis with activated microglia fulfilled the diagnostic criteria for RE in our case [4].

According to the new ILAE classification system of FCD [22], FCD type IIIId is associated with lesions acquired during early life, i.e., traumatic brain injury, glial scarring after prenatal or perinatal ischemic injury or bleeding, and inflammatory or infectious diseases. Wang et al. identified four patients with RE and FCD type IIIId [15]. This finding further supports a role for the concept of acquired and postmigrational pathomechanisms in the etiology of FCDs [23].

Little has been offered to explain the presence of dual pathology. One hypothesis suggests that the focal cortical dysplasia may cause alterations in the blood–brain barrier, allowing circulating antibodies, antigens, and inflammatory cells access to the brain and promoting development of Rasmussen's encephalitis [13]. Another explanation could be that neurogenesis may be induced by seizures produced by Rasmussen's encephalitis resulting in a cortical dysplasia in the affected area [13].

Results of focal resections in patients with RE are disappointing. Hemispherectomy, a surgical procedure for total or partial removal of a cerebral hemisphere, is considered a highly effective therapy to achieve seizure control in RE [4]. Either anatomical or functional hemispherectomy has been proposed [24,25]. Anatomical hemispherectomy has largely been abandoned because of postoperative mortality caused by hydrocephalus, hemosiderosis, and trivial head traumas [26]. The goal of hemispherectomy is to achieve complete seizure control, promote neurodevelopmental progress in the unaffected contralateral hemisphere, and avoid seizure-related comorbidities. In our case, the mapped seizure onset zone overlapped the eloquent motor and sensory cortex. As the family was unwilling to proceed with a hemispherectomy but was keen for more limited surgical intervention, we opted to perform a partial cortical resection and multiple sub

pial transections in order to limit any motor deficits. While this surgery appears to have reduced the severity of EPC three months postoperation, it is likely that she will require a more definitive hemispherectomy in the future.

Conflict of interest statement

The authors have no conflict of interests in the publication of this report to reveal.

References

- [1] Dulac O. Rasmussen's syndrome. *Curr Opin Neurol* 1996;9:75–7.
- [2] Bien CG, Urbah H, Wiestler OD, Lassmann H, Elger CE, Deckert M. Diagnosis and staging of Rasmussen's encephalitis by serial MRI and histopathology. *Neurology* 2002;58:250–7.
- [3] Bien CG, Widman G, Urbah H, Sassen R, Kuczaty S, Wiestler OD, et al. The natural history of Rasmussen's encephalitis. *Brain* 2002;125:1751–9.
- [4] Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis. A European consensus statement. *Brain* 2005;128:454–71.
- [5] Hart YM, Cortez M, Andermann F, Hwang P, Fish DR, Dulac O, et al. Medical treatment of Rasmussen's syndrome (chronic encephalitis and epilepsy): effect of high-dose steroids or immunoglobulins in 19 patients. *Neurology* 1994;44:1030–6.
- [6] Maria BL, Ringdahl DM, Mickle JP, Smith LJ, Reuman PD, Gilmore RL, et al. Intraventricular alpha interferon therapy for Rasmussen's syndrome. *Can J Neurol Sci* 1993;20:333–6.
- [7] Andrews PI, Dichter MA, Berkovic SF, Newton MR, McNamara JO. Plasmapheresis in Rasmussen's encephalitis. *Neurology* 1996;46:242–6.
- [8] Rasmussen T, Olszewski J, Lloydsmith D. Focal seizures due to chronic localized encephalitis. *Neurology* 1958;8:435–45.
- [9] Bien CG, Bauer J, Deckwerth TL, Wiendl H, Deckert M, Wiestler OD, et al. Destruction of neurons by cytotoxic T cells: a new pathogenic mechanism in Rasmussen's encephalitis. *Ann Neurol* 2002;51:311–8.
- [10] Takei H, Wilfong A, Malphrus A, Yoshor D, Hunter JV, Armstrong DL, et al. Dual pathology in Rasmussen's encephalitis: a study of seven cases and review of the literature. *Neuropathology* 2010;30:381–91.
- [11] Yacubian EMT, Rosemberg S, Marie SKN, Valério RMF, Jorge CL, Cukiert A. Double pathology in Rasmussen's encephalitis: etiologic considerations. *Epilepsia* 1996;37:495–500.
- [12] Cheong JY, Wong C, Bleasel A, Varikatt W, Ng T, Dexter MA. Late onset Rasmussen's encephalitis with triple pathology. *J Clin Neurosci* 2009;16:1677–81.

- [13] Palmer CA, Geyer JD, Keating JM, Gilliam F, Kuzniecky RI, Morawetz RB, et al. Rasmussen's encephalitis with concomitant cortical dysplasia: the role of GluR3. *Epilepsia* 1999;40:242–7.
- [14] Prayson RA. Dual pathology in Rasmussen's encephalitis: a report of coexistent focal cortical dysplasia and review of the literature. *Case Rep Pathol* 2012;2012.
- [15] Wang D, Blümcke I, Gui Q, Zhou W, Zuo H, Lin J, et al. Clinico-pathological investigations of Rasmussen encephalitis suggest multifocal disease progression and associated focal cortical dysplasia. *Epileptic Disord* 2013;15:32–43.
- [16] Hart YM, Andermann F, Robitaille Y, Laxer KD, Rasmussen T, Davis R. Double pathology in Rasmussen's syndrome: a window on the etiology? *Neurology* 1998;50:731–5.
- [17] Bittner S, Simon OJ, Göbel K, Bien CG, Meuth SG, Wiendl H. Rasmussen encephalitis treated with natalizumab. *Neurology* 2013;81(4):395–7.
- [18] Chiapparini L, Granata T, Farina L, Ciceri E, Erbetta A, Ragona F, et al. Diagnostic imaging in 13 cases of Rasmussen's encephalitis: can early MRI suggest the diagnosis? *Neuroradiology* 2003;45:171–83.
- [19] Granata T, Gobbi G, Spreafico R, Vigeveno F, Capovilla G, Ragona F, et al. Rasmussen's encephalitis: early characteristics allow diagnosis. *Neurology* 2003;60:422–5.
- [20] Chinchilla D, Dulac O, Robain O, Plouin P, Ponsot G, Pinel JF, et al. Reappraisal of Rasmussen's syndrome with special emphasis on treatment with high doses of steroids. *J Neurol Neurosurg Psychiatry* 1994;57:1325–33.
- [21] Tobias SM, Robitaille Y, Hickey WF, Rhodes CH, Nordgren R, Andermann F. Bilateral Rasmussen encephalitis: postmortem documentation in a five-year-old. *Epilepsia* 2003;44:127–30.
- [22] Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, et al. The clinico-pathological spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 2011;52:158–74.
- [23] Spreafico R. Are some focal cortical dysplasias post-migratory cortical malformations? *Epileptic Disord* 2010;12:169–71.
- [24] Villemure JG. Anatomical to functional hemispherectomy from Krynauw to Rasmussen. *Epilepsy Res Suppl* 1992;5:209–15.
- [25] O'Brien DF, Basu S, Williams DH, May PL. Anatomical hemispherectomy for intractable seizures: excellent seizure control, low morbidity and no superficial cerebral haemosiderosis. *Childs Nerv Syst* 2006;22:489–98 [discussion:99].
- [26] De Almeida AN, Marino Jr R, Aguiar PH, Jacobsen Teixeira M. Hemispherectomy: a schematic review of the current techniques. *Neurosurg Rev* 2006;29:97–102.