

# Chronic T Cell Encephalitis Responsive to Immunotherapy

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## Abstract

Chronic encephalitis manifesting as an epilepsy syndrome most commonly presents as Rasmussen's syndrome, usually characterized by epilepsy partialis continua, hemiparesis, and progressive cortical deficits such as aphasia, hemianopia, and cognitive decline. It is characterized by progressive hemispheric cortical atrophy on imaging and is usually seen in childhood. Adult-onset of the syndrome is rare, and only a few cases have been reported with bilateral symptoms. We present a patient with pseudobulbar affect and frontal lobe dysfunction who developed multifocal myoclonic jerks, right hemibody focal motor seizures, and right hemiparesis with bilateral cerebellar signs. Magnetic resonance imaging showed progressive hemispheric atrophy and bilateral features in Positron emission tomography-computed tomography (PET CT). Brain biopsy revealed chronic T-cell infiltrate. We discuss this case as the patient had several features that were atypical for Rasmussen's encephalitis (or syndrome).

**Keywords:** Chronic T cell encephalitis, epilepsy partialis continua, Rasmussen encephalitis

## INTRODUCTION

Chronic encephalitis manifesting as an epilepsy syndrome most commonly presents as Rasmussen's syndrome characterized by epilepsiapartialis continua, hemiparesis, and progressive cortical deficits such as aphasia, hemianopia, and cognitive decline. There is progressive hemispheric cortical atrophy on imaging and is usually seen in childhood. This syndrome is typically associated with chronic T-cell encephalitis on histopathological examination of brain tissue.<sup>[1]</sup> Adult-onset of the syndrome is rare, and only a few cases have been reported with bilateral symptoms.<sup>[2]</sup> We discuss this case as the patient had atypical features for Rasmussen's syndrome and resembled other autoimmune encephalitis syndromes.

## CASE REPORT

A 25-year-old male with no comorbidities presented with 6 months history of behavioral change and pseudobulbar affect characterized by excessive laughing and crying, overall reduced speech output, and withdrawal from social interactions. This was preceded by recurrent episodes of vomiting and dizziness. Over the next 2 weeks, he also developed frequent oral chewing movements, shaking the head, and recurrent semi-purposeful scratching movements involving his right upper limb. He was disinhibited and once came out of the bathroom without any clothes. About 15 days after these behavioral changes, he started experiencing more rhythmic jerking of the right upper limb. Around that time, he also developed right-hand weakness limiting his ability to feed himself. The frequency of these jerks started increasing, and over the next month, he started having jerking of the right lower limb, associated with progressive right hemiparesis. Over the next 3–4 months, he lost the ability to walk independently due to his right lower

limb weakness. By then, he also developed dysarthria and dysphagia with drooling.

He did not have systemic complaints, rashes, joint pains, redness of eyes, or nodules anywhere in the body. His past history was significant for a penile ulcer 4 years back, and his wife also had a genital ulcer for which both were treated and had been cured with medications.

On examination, he was alert, and despite his limited speech output, he appeared oriented to person but not to place or time. General examination was within normal limits. He was not cooperative for cognitive assessment due to a lack of attention. He had a gaze preference to the left side and nystagmus with a fast component to the left side. He had bifacial upper motor neuron type weakness, more on the right side. Features of aphasia included reduced comprehension and reduced communication ability. Spastic dysarthria and other features of pseudobulbar palsy were present. He had right-sided epilepsy partialis continua involving the face, upper and lower limbs with stimulus-sensitive myoclonic jerks, with a clear rotational

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component mainly at the wrist joint, suggesting facio-brachial dystonic seizures [Video 1]. He had right hemiparesis and bilateral cerebellar signs. The rest of the systemic examination was normal.

### Localization and differential diagnosis

The localization was made to the frontal cortex in view of withdrawn behavior, speech, and language abnormalities more prominent left side involvement in view of right focal seizures [Video 1] and cortical myoclonus as well as hemiparesis; and to bilateral subcortical white matter in view of pseudobulbar affect. Bilateral fronto-ponto-cerebellar tracts or cerebellar involvement would explain the cerebellar signs. Electroencephalography (EEG) revealed the left onset with fast activity fronto-centrotemporal leads [Figure 1]. Possible causes of *epilepsia partialis continua* (EPC) are stroke, structural lesions such as a tuber, infections such as neurocysticercosis, tuberculomas, tumors were considered, and brain imaging was done [Figure 2], which ruled out these differentials. Non-ketotic hyperglycemia and mitochondrial encephalopathy could also present with EPC, but blood sugar and other biochemical investigations were not consistent with these possibilities. Rasmussen's encephalitis spectrum was considered, and a biopsy from the left frontal lobe was done. Histopathology showed a chronic T-cell encephalitis [Figure 3]. So based on the clinical picture of rapidly progressive neurologic deficits, facio-brachial EPC, and imaging, a possibility of Rasmussen's encephalitis was raised. In view of initial symptoms of apathy and social withdrawal with facio brachial seizures, other causes such as autoimmune encephalitis like leucine-rich glioma inactivated 1 (LG-I1) associated disease,<sup>[3]</sup> lymphoma, Hashimoto's

encephalitis, CNS vasculitis, neuropsychiatric lupus, neurosyphilis, tuberculosis, celiac disease were considered and investigated accordingly.

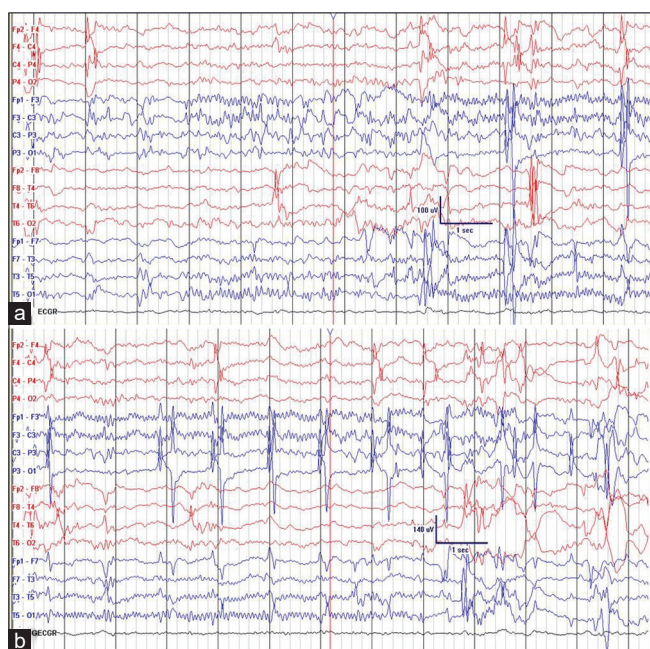
The hemogram, peripheral smear, erythrocyte sedimentation rate, C-reactive peptide were within normal limits. HIV, anti Hepatitis C virus (HCV), hepatitis B surface antigen, and serum Venereal disease research laboratory test (VDRL) were negative. Antinuclear antibody, antineutrophil cytoplasmic antibody, and antithyroperoxidase (TPO) antibody were negative. Cerebrospinal fluid (CSF) was noninflammatory with five cells, protein of 37 mg/dL, glucose of 65 mg/dL, and corresponding blood glucose of 104 mg/dL. The rest of the CSF investigations, such as VDRL, *Treponema pallidum* hemagglutination (TPHA), cytospin for malignant cytology, polymerase chain reaction for herpes simplex virus (HSV) (HSV PCR), CSF autoantibody profile including anti N-methyl-d-aspartate (NMDA), LGI-1, and glutamic acid decarboxylase 65-kilodalton isoform (GAD-65), were negative. Based on histopathologic features suggestive of chronic T-cell encephalitis, possibilities of Rasmussen's encephalitis, chronic viral infection such as chronic herpes infection, paraneoplastic encephalitis, and autoimmune encephalitis were considered. However, histopathology was not suggestive of viral inclusions, CSF autoimmune profile was negative, though a limited panel was performed, and positron emission tomography-computed tomography (PET-CT) did not reveal systemic malignancy. PET brain was suggestive of bilateral encephalitis [Figure 4]. Anti Glutamate receptor type 3 and anti Munc18 antibodies were planned to be sent; however, they were not done due to financial constraints.

### Treatment and outcome

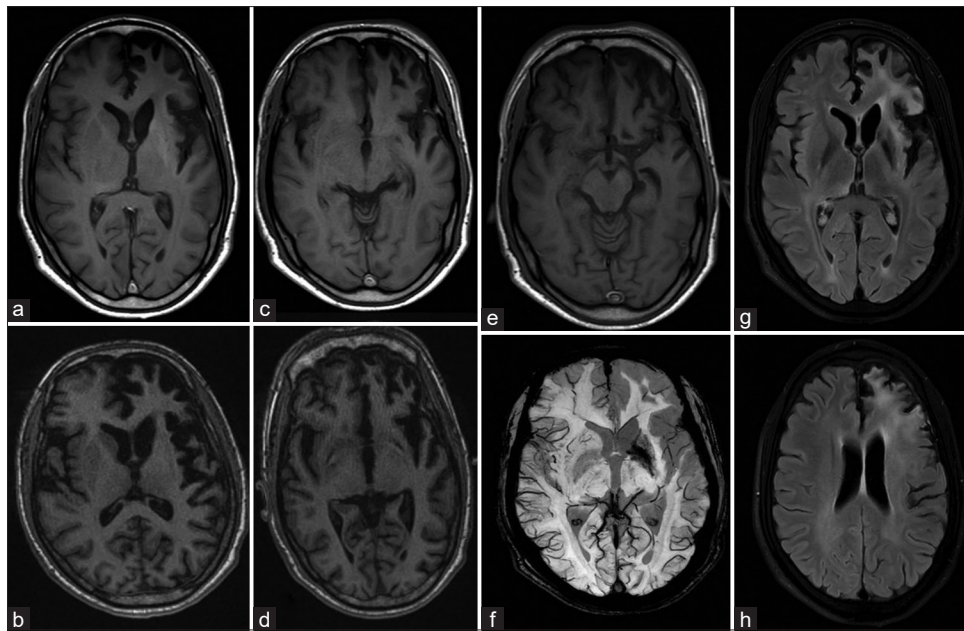
His seizures were not controlled with anti-seizure medications. At presentation, his power in the right upper limb was 4/5, and his right-hand grip was 80%. However, over the next month, he had rapidly worsening weakness (Power 1/5 with handgrip of 20%). As he had rapidly progressive symptoms without much response to intra-venous methylprednisone, he was initiated on plasma exchange.<sup>[4]</sup> After plasma exchange, there was a marked improvement with seizure control and improvement in power. He could walk a few steps without support within 3 days of starting the plasma exchange. Seizure frequency also decreased significantly, power improved to 4-/5, and he was discharged. Three months later, there was worsening weakness, and he received another cycle of plasma exchange with partial improvement. We planned a repeat antibody panel, now including anti- glutamate receptor (GluR3). However, he did not show up for his follow-up visits. When contacted over the phone after 3 months to ask regarding the patient's status, we were informed that the patient had died. The cause was probably aspiration due to bulbar dysfunction.

### DISCUSSION

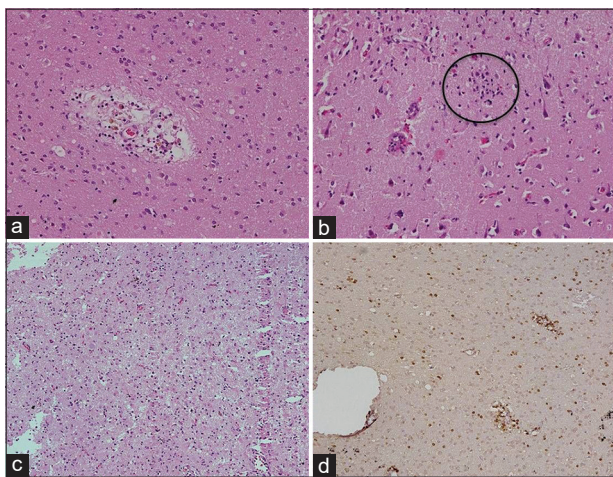
Clinically, our patient's presentation was consistent with that of autoimmune encephalitis. Presenting features, especially



**Figure 1:** (a) Shows ictal in the left onset with fast activity fronto-centrotemporal leads (b) Continuation of ictal discharges and then return to baseline in the last 2 s



**Figure 2:** (a, c, e) T1-weighted imaging showing asymmetric atrophy left > right frontotemporal lobes; (b and d) corresponding sections of brain imaging showing progression in the atrophy 2 months later. The right frontotemporal lobes have also started shrinking with the prominence of Sylvian fissure and the gyri and sulci. (f) Susceptibility-weighted image showing hemorrhage in the left globus pallidus. (g) and 2-h showing frontotemporal atrophy and gliosis of the subcortical white matter in the left frontal and bilateral parieto-occipital regions. (b and d) are images 2 months after the rest of the images



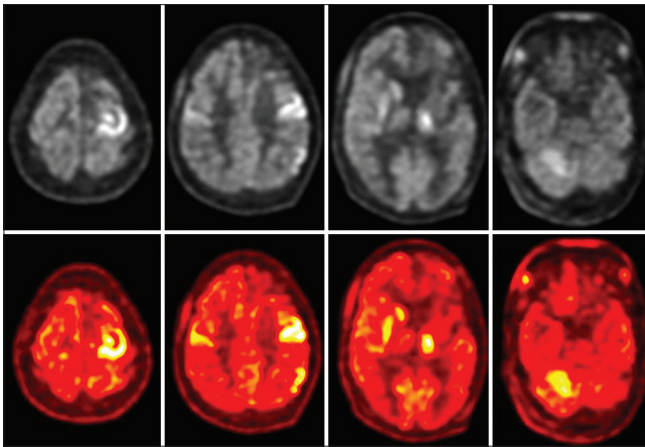
**Figure 3:** (a) Perivascular chronic inflammation and cuffing by lymphocytes, (b) Microglial nodule (marked) with surrounding neurons showing ischaemic change (red neurons), (c) glial scarring/gliosis, (d) Predominance of CD3 positive lymphocytes

seizure semiology and imaging features, were very similar to those described in a large series of anti-leucine-rich glioma-inactivated 1 (*LG1*). However, as our patient tested negative for antibodies, and the biopsy revealed features of chronic T-cell encephalitis, we diagnosed him with Rasmussen's syndrome. Three cases of chronic focal encephalitis were described in 1958 by Rasmussen *et al.*<sup>[5]</sup> with a detailed pathologic description. These cases did not have MRI or CT images. The diagnosis of Rasmussen's encephalitis was made based on composite criteria, including clinical features of EPC or progressive hemispheric deficits, progressive

unihemispheric cortical atrophy, and histopathology suggestive of chronic T-cell lymphocytic infiltration, gliotic nodules, and perivascular lymphocytic cuffing. These criteria were proposed in 2004 in the European congress on epileptology and were published by Bien *et al.*<sup>[11]</sup> As seen in this consensus statement, none of the criteria in isolation is diagnostic of Rasmussen's encephalitis. It has also been seen that only 50% of patients with RE have EPC as the presenting symptom.<sup>[6,7]</sup> Based on the site of inflammation, patients may have aphasia, hemianopia, and other deficits. However, in our patient, the initial clinical features were apathy and decreased speech along with pseudobulbar features, which have not been reported so far. Rasmussen's encephalitis is a disease of childhood, and in a series of 18 patients reported by Pradeep *et al.*,<sup>[6]</sup> the age of onset ranged from 1.5 years to 18 years in 17 patients with only one patient aged more than 18 years at onset. However, our patient was 25 years old at the onset of symptoms. All the 17 patients whose MRI was available for analysis in the series by Pradeep *et al.*,<sup>[6]</sup> had unilateral features as opposed to our patient, who had bilateral features on MRI and PET CT.

Our patient had documented progression of bilateral hemispheric atrophy, which was asymmetrical and was more on the left side. Bilateral clinical and imaging involvement in Rasmussen's encephalitis is rare and reported in a few case series and reports.<sup>[2,7-10]</sup>

Histopathologically, it was a T-cell-dominated encephalitis with CD3 positive T-cells. Chronic T-cell encephalitis may be due to viral (herpes, Epstein-Barr virus (EBV), Cytomegalovirus (CMV), West Nile, etc.) or antibody-mediated [autoimmune (anti N-methyl-D-aspartate



**Figure 4:** 18FDG PET/CT performed 60 min post tracer injection revealed atrophy of the left frontal area with increased radiotracer uptake in the posterior margins of the frontoparietal cortices. The left head of the caudate nucleus is not seen, probably atrophic. There are bilateral multiple cortical increased uptakes, namely left thalamus, right striatum, and right cerebellum. The findings are consistent with b/l encephalitis

receptor (NMDA), voltage-gated potassium channel (VGKC), *generalized anxiety disorder* (GAD) or glycine receptors (GlyR) or paraneoplastic (anti-Ma-1, Ma-2, Hu, Yoetc)<sup>[11]</sup> The pathogenesis of Rasmussen's encephalitis seems to be enigmatic with viral etiology and autoimmune etiology competing with each other. One hypothesis is that certain focal viral infections of the cerebral parenchyma lead to granzyme-mediated cytotoxic T-cell attacks on the neurons. However, no specific virus has been proven so far to incite RE. Another hypothesis is that T-cell inflammation is primary.<sup>[1]</sup> Humoral immunity due to multiple suspect antibodies against Glutamate receptor-3 (GluR3), anti Syntaxin-binding protein 1(-Munc-18), and alpha-7 nicotinic acetylcholine receptors are also being studied. These antibodies are not present in all patients, and not all of them respond to plasma exchange.<sup>[12]</sup>

The disease duration from onset to diagnosis was 6 months to 18 years in the series by Pradeep *et al.*,<sup>[6]</sup> Our patient had a relatively rapid and fulminant course, and onset to diagnosis was 7 months. Unfortunately, the patient died around 1 year after the disease onset.

## CONCLUSION

Rasmussen's encephalitis is thus a rare diagnosis in adults and should always be considered in the differential diagnosis of patients with refractory seizures and hemiparesis. Identifying the disease may be difficult in patients who present with cognitive symptoms and may be delayed until seizures and hemiparesis uncover the diagnosis. Though RE was highly probable in our patients, other etiologies such as autoimmune encephalitides, chronic viral encephalitis due to CMV, EBV,

West Nile virus, etc., cannot be ruled out with certainty as polymerase chain reaction (PCR) testing for these viruses could not be conducted. In addition, immunosuppression could alter the natural history of the disease, and early aggressive therapy might be needed in patients with Rasmussen's encephalitis.

## Learning points

- Chronic T-cell encephalitis responsive to immunotherapy may be due to viral, autoimmune, or paraneoplastic causes.
- Rasmussen's encephalitis can occur in adults and should be considered in patients with focal seizures and progressive hemiparesis.
- Bilateral involvement in Rasmussen's encephalitis is a rare presentation and could be confirmed with a biopsy.
- While it usually has a long chronic course and usually responds to immunotherapy, it may rarely also be fatal.

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## Conflicts of interest

There are no conflicts of interest.

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