Triple Pathology in Rasmussen's Encephalitis: A New Pathological Phenotype

Dear Editor,

Rasmussen's encephalitis (RE) was first described in 1958 by Rasmussen[1] and his colleagues as a very rare and chronic neurological disorder characterized by unilateral cerebral inflammation. Although diagnostic criteria have been framed [Table 1], the definite underlying pathophysiology is yet to be elucidated. Immunological mechanisms are postulated most consistently[2] but an association with other chronic epileptogenic pathologies has also been described. We present a case report of an adult-onset Rasmussen's encephalitis with immunological pathology along with focal cortical dysplasia and hippocampal sclerosis.

A 30-year-old gentleman presented with history of right focal motor seizures without loss of consciousness since the past 8 years. He was initially treated with anti-epileptic drugs with good seizure control and occasional breakthrough seizures (once in a few months, despite treatment). Thereafter, he discontinued treatment 4 years back following which he started having daily seizures and also developed behavioral changes. He became disinhibited and started using obscene words and gestures, had episodes of violent outbursts, and occasionally had urinary incontinence without embarrassment.

Table 1: Diagnostic Criteria for Rasmussen's encephalitis

PART A (ALL THREE)
1. Clinical: Focal seizures (with or without epilepsia partialis continua) and unilateral cortical deficits
2. EEG: Unihemispheric slowing with or without epileptiform discharges
3. MRI: Unihemispheric focal cortical atrophy and at least one of the following:
Grey or white matter T2/FLAIR hyperintense signal
Hyperintense signal or atrophy of the ipsilateral caudate head
OR Part B (two of three)
1. Clinical: Epilepsia partialis continua or progressive* unilateral cortical deficits
2. MRI: Progressive* unihemispheric focal cortical atrophy
3. Histopathology: T cell-dominated encephalitis with activated microglial cells typically, but not necessarily, forming nodules and reactive astrogliosis; numerous parenchymal macrophages, B cells, or plasma cells or viral inclusion bodies exclude the diagnosis of Rasmussen's encephalitis

He presented to us at this time with multiple seizures per day and was found to have motor aphasia with perseveration, right sided grade 1 spasticity in limbs with 4/5 power (on MRC scale) with hyperreflexia and extensor plantar. Left sided examination was normal. A neuropsychological assessment was suggestive of profound intellectual impairment and social maladaptation, functionally equivalent to a 1.5-year-old child. A clinical possibility of RE was considered and magnetic resonance imaging (MRI) of the brain revealed left hemispheric atrophy with head of caudate and putamen involvement, and dilatation of frontal horn of ipsilateral lateral ventricle [Figure 1a]. Electroencephalogram (EEG) was suggestive of left frontal predominant spike and wave discharges [Figure 1b]. The patient fulfilled the diagnostic criteria of RE and therapeutic options of plasma exchange and hemispherotomy were explained to the family members. Five cycles of plasma exchange were done (surgery refused) following which his seizure frequency decreased to 1–2 per week; but his right-sided weakness and behavioral issues persisted. All three complaints started increasing again after 2 months and the patient presented with epilepsia partialis continua (EPC) 4 months later. He was treated with additional pulse steroids and intravenous immunoglobulins and repeat MRI Brain was suggestive of increased atrophy in the left perisylvian region, left caudate and putamen. EEG showed discharges localized predominantly to the left frontal lobe. Positron Emission Topography-Computed Topography (PET-CT) also localized to left frontal and opercular region. Thereafter, the patient underwent a functional left hemispherotomy with left temporal lobectomy and the histopathological examination revealed loss of neurons in the pyramidal layer and granular layer of

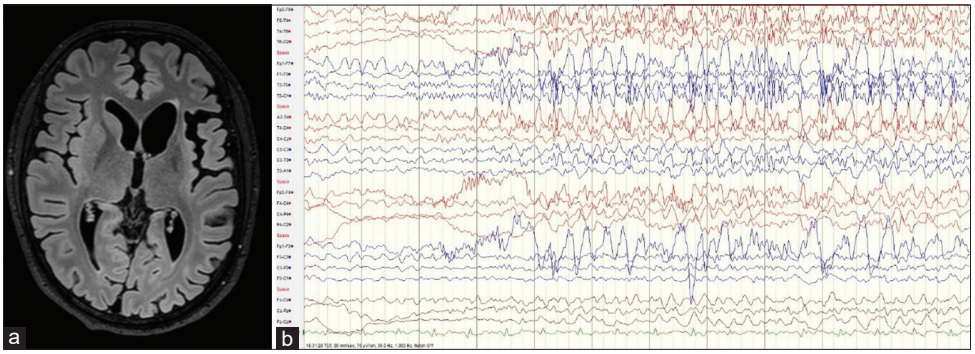

Figure 1: (a) MRI Brain demonstrating left hemispheric atrophy (predominantly perisylvian, caudate and putamen). (b) EEG showing 3.5–4 Hz spike and wave discharges and polyspikes localised to the left frontal lobe

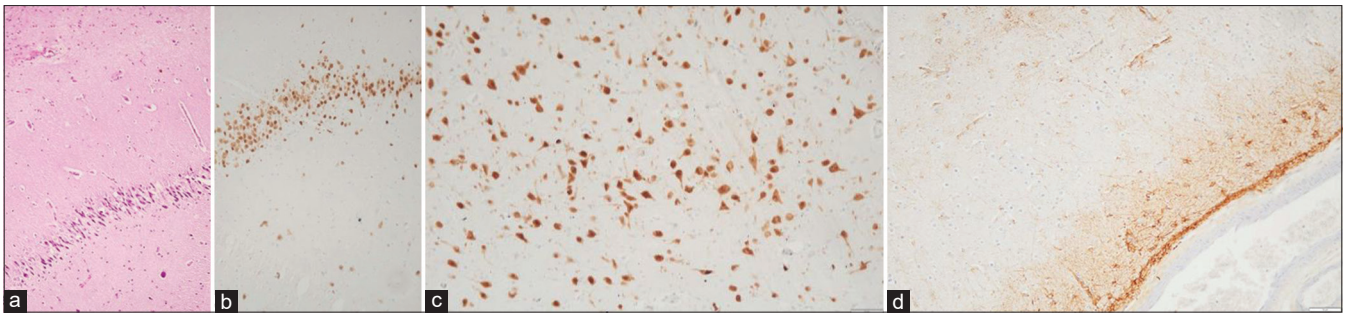

Figure 2: Histopathological specimen. (a) H and E stain from hippocampus, shows loss of neurons and ischemic changes in neurons at pyramidal layer. (b) Neu-N immunostain highlights the dispersion of neurons at pyramidal layer. (c) Neu-N immunostain highlights the cortical dyslamination of neurons and loss of neurons with ischemic changes. (d) GFAP immunostain highlights the supial gliosis

temporal lobe with concomitant ischemic changes and cortical dyslamination suggestive of focal cortical dysplasia (FCD) type IIIa with hippocampal sclerosis [Figure 2a-d].

There was marked reduction in the seizure frequency post-operatively but the patient had a residual right-sided weakness with a seizure frequency of 1–2 per week on antiseizure drugs. This particular combination of RE with FCD along with hippocampal sclerosis is very rare and has not been reported to our knowledge. Our case highlights a new plausible clinicopathological association of RE.

RE is characterized by drug resistant focal epilepsy and progressive neurological and cognitive deterioration. It usually affects children and young adults and is rare, with an incidence of 2.4 cases per 10 million aged 18 years or younger.[3,4] Typical symptoms consist of a prodrome of infrequent seizures (prodromal stage) followed by frequent ones, and progressive hemiparesis (active stage) and if untreated, cognitive decline and hemianopia with the spread of the pathology.[2] Refractory focal status epilepticus occurs in around 50% of patients.[5] Rare manifestations include chorea, dystonia[6] and progressive neurological deficit sans seizures.[7-9] Although, the exact pathophysiology is debatable, histopathological examination demonstrating cortical inflammatory cells (T lymphocytes), neuronal loss, gliosis and microglial nodules is the gold standard for diagnosis.[10] MRI Brain characteristically demonstrates unilateral hemispheric atrophy with atrophy of caudate.[10] However, it needs to be differentiated from other unihemispheric epileptic syndromes like cortical dysplasia, tuberous sclerosis and Sturge-Weber Syndrome. There is no definitive cure, with immunotherapy reported to halt the progression of disease temporarily and the only palliative option being surgeries like functional hemispherotomy and hemispherectomy. Their opportune timing is still under debate.[2]

Association between RE and other causes of chronic drug-resistant conditions is known but is a rare finding. The same was first reported in 1996 by Yacubian *et al*.[11] in a 7-year-old girl with concomitant FCD. Subsequently various other studies have reported an association with other conditions like tuberous sclerosis, tumours (Gangliolioma, Astrocytoma) and vascular malformation.[12] The most common association has been reported with FCD (especially Type I) with a reported prevalence of around 10%.[13] Only one case of triple pathology has been reported which was in a 27-year-old male with late-onset Rasmussen's encephalitis in association with old ischemic changes and Type II FCD.[14] Various possible explanations have been proposed for the association between RE and other structural abnormalities with one particular mechanism being that alterations in the blood–brain barrier leading to infiltration of pathogenic antibodies and subsequent development of RE.[13] Another plausible reasoning is that continuous seizure activity in RE may lead to dysplastic neurogenesis resulting in cortical dysplasia.[13] Interestingly in the study done by Takei *et al*.[13] involving 7 patients, there was co-occurrence of concomitant pathologies in all 7 cases, leading them to propose that the same is underappreciated and requires more careful pathological studies. Most of the cases had no previous suspicion of a dual pathology based on pre-operative neuroimaging and the same was only elucidated on biopsy, underlining the importance of the same. Nevertheless, the association between two rare chronic epilepsy pathologies appears not to be by chance and might have implications for elucidating underlying mechanisms, definitive treatment and surgical procedures.[13]

In our particular case, clinic-radiological definitive Rasmussen's was associated with FCD type IIIa and hippocampal sclerosis. Careful pathological examination of operated RE cases might lead to further identification of similar cases and might lead to better understanding of this scarcely understood rare chronically progressive debilitating entity.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Ayush M. Makkar, Snigdha Komakula, Ayush Agarwal, Saumya Sahu[1], Vaishali Suri[1], Achal K. Srivasatava

Departments of Neurology and [1]Neuropathology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Dr. Ayush Agarwal, Department of Neurology, AIIMS, New Delhi, India.
E-mail: ayushthetaurian@gmail.com

References

1. Rasmussen T, Olszewski J, Lloyd-Smith D. Focal seizures due to chronic localized encephalitis. Neurology 1958;8:435-45.
2. Varadkar S, Bien CG, Kruse CA, Jensen FE, Bauer J, Pardo CA, *et al*. Rasmussen's encephalitis: Clinical features, pathobiology, and treatment advances. Lancet Neurol 2014;13:195-205.
3. Lamb K, Scott WJ, Mensah A, Robinson R, Varadkar S, Cross J. Prevalence and clinical outcome of Rasmussen encephalitis in children from the United Kingdom. Dev Med Child Neurol 2013;55(Suppl 1):14.
4. Ramesha KN, Rajesh B, Ashalatha R, Kesavadas C, Abraham M, Radhakrishnan VV, *et al*. Rasmussen's encephalitis: Experience from a developing country based on a group of medically and surgically treated patients. Seizure 2009;18:567-72.
5. Longaretti F, Dunkley C, Varadkar S, Vargha-Khadem F, Boyd SG, Cross JH. Evolution of the EEG in children with Rasmussen's syndrome. Epilepsia 2012;53:1539-45.
6. Frucht S. Dystonia, athetosis, and epilepsiapartialis continua in a patient with late-onset Rasmussen's encephalitis. Mov Disord 2002;17:609-12.
7. Bien CG, Elger CE, Leitner Y, Gomori M, Ran B, Urbach H, *et al*. Slowly progressive hemiparesis in childhood as a consequence of Rasmussen encephalitis without or with delayed-onset seizures. Eur J Neurol 2007;14:387-90.
8. Ravindra VM, Mazur MD, Mohila CA, Sweney MT, Hersh A, Bollo RJ. Rasmussen encephalitis with dual pathology in a patient without seizures: Case report and literature review. Childs Nerv Syst 2015;31:2165-71.
9. Garg D, Agarwal A, Dash D, Mahajan S, Singh RK, Bhatia R, *et al*. Rasmussen's encephalitis presenting as progressive parietal dysfunction sans seizures. Seizure 2019;71:219-21.
10. Olson HE, Lechpammer M, Prabhu SP, Ciarlini PD, Poduri A, Gooty VD, *et al*. Clinical application and evaluation of the Bien diagnostic criteria for Rasmussen encephalitis. Epilepsia 2013;54:1753-60.
11. Yacubian EMT, Rosemberg S, Marie SKN, Valerio RMF, Jorge CL, Cukiert A. Double pathology in Rasmussen's encephalitis: Etiologic considerations. Epilepsia 1996;37:495-500.
12. 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.
13. Takei H, Wilfong A, Malphrus A, Yoshor D, Hunter JV, Armstrong DL. Dual pathology in Rasmussen's encephalitis: A study of seven cases and review of the literature. Neuropathology 2010;30:381-91.
14. 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.

Submitted: 14-Sep-2021 **Accepted:** 10-Nov-2021 **Published:** 14-Feb-2022

DOI: 10.4103/aian.aian_815_21