A bird eye view on Rasmussen Encephalitis


Meghraj Suryawanshi[1,3] , Pranjal Gujarathi[2,4] *

[1]Department of Pharmaceutics and Pharmaceutical Technology, Krishna School of Pharmacy and Research, Drs. Kiran and Pallavi Patel Global University (KPGU), Varnama, Vadodara, Gujarat-391240

[2]Department of Pharmacology, Vidhyadeep Institute of Pharmacy, Vidhyadeep University, Anita, Surat, Gujarat-394110

[3]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan-302017

[4]Research scholar, Bhagwan Mahavir Centre for Advanced Research & Bhagwan Mahavir College of Pharmacy, Bhagwan Mahavir University, Vesu, Surat, Gujarat-395007

Email: pranjalgujarathi19@gmail.com

Abstract

Rasmussen encephalitis (RE) is a rare and progressive neurological disorder primarily affecting children, characterized by chronic inflammation and unilateral brain atrophy. Diagnosis relies on clinical, electroencephalogram (EEG), magnetic resonance imaging (MRI), and histopathological criteria. Current treatments, including high-dose methylprednisolone, intravenous immunoglobulin's (IVIg), and surgical interventions such as hemispherectomy, offer varying degrees of success in managing seizures and slowing disease progression. Adalimumab has shown efficacy in reducing seizure frequency. Ongoing patent activity underscores efforts to develop novel therapies. Enhanced research is essential to improve diagnostic precision and treatment outcomes for RE patients. Keywords: Rasmussen encephalitis, diagnosis, treatment, seizures, hemispherectomy, adalimumab, patents, neurological disorder.

Keywords: Rasmussen encephalitis, Immunotherapy, Pathophysiology, Patents

1. Introduction

Rasmussen encephalitis (RE), first identified in 1958 by Theodore Rasmussen, is characterized by chronic inflammation of one hemisphere of the brain, leading to unilateral atrophy (1). This condition typically affects healthy school-aged children and is marked by persistent, medication-resistant focal seizures along with worsening neurological and cognitive deficits associated with the affected brain hemisphere. The disease significantly impacts patients and their families (1). Despite being recognized for approximately six decades, our understanding of RE remains limited, and available treatment options are still rudimentary. Due to the progressive nature of RE, early detection and diagnosis are essential for utilizing both current and emerging treatment strategies (2).

RE, also known as Rasmussen syndrome, is a rare central nervous system disorder marked by chronic, progressive inflammation of one cerebral hemisphere (3). This condition typically leads to frequent

epileptic seizures caused by uncontrolled electrical activity in the brain and gradual cerebral deterioration. Over time, additional symptoms may develop, such as progressive hemiparesis, language difficulties (if the left hemisphere is affected), and intellectual disabilities (3). The exact cause of RE remains unclear, but two leading theories suggest that brain inflammation might be either a response to a foreign antigen (infection) or an autoimmune disease confined to one side of the brain, leading to damage. RE primarily affects children aged two to ten, with the disease being most severe in the first 8 to 12 months. After reaching its peak inflammatory stage, the disease's progression usually slows or halts, leaving the patient with lasting neurological deficits (4). This article provides an updated overview of RE, detailing recent advances in understanding its pathogenesis and emphasizing clinical aspects critical to its diagnosis and management.

2. Clinical presentation

Rasmussen's Encephalitis (RE) is portrayed by uni-hemispheric brain shrinkage, focal drug-resistant epilepsy, developing hemiplegia, and deterioration of cognitive functions. RE generally starts in childhood or young adults with a mean age of 6 years at the time of presentation, in a previously healthy child. Seizures are often preceded by slowly progressive hemiparesis, hemidistonia, or hemiathetosis (5).

In most instances, seizures are polymorphic: in addition to simple motor seizures, there are almost all types of focal seizures that can occur. Seizure frequency that are resistant to antiepileptic drugs (AEDs) usually increases rapidly, and partial epilepticus may return. Epilepsia partialis cotinua (EPC) occurs in approximately half of children (5). During the illness, hemiparesis inevitably develops; at first, it is restricted to the postictal phase, but it quickly becomes permanent, albeit with varied severity, and it gets worse with increased seizure activity. Hemiparesis, which could include a dystonic component, stabilizes over time. Additionally, When the dominant hemisphere is compromised, symptoms include aphasia, cortical sensory loss, and hemianopia are developed (5,6). Like motor weakness, cognitive impairment is a consistent hallmark of RE and may initially be mild. Changes in behavior, such as irritation, emotional instability, or hyperactivity, frequently indicate the onset of mental illness. This includes learning disabilities as well as memory and attention issues. In the majority of patients, the degree of mental impairment appears to be correlated with how severe their epilepsy is, especially when it is related to the bilateral distribution of abnormalities in their EEG (5,6).

The sickness is progressing unabatedly. The natural history can be categorized into three stages: (1) a "prodromal stage," which lasts for months to eight years and is characterized by infrequent seizures; (2) an "acute stage," which often occurs close to the beginning of the disease and is characterized by frequent seizures, frequently in the form of EPCorstatus, and rapid neurological degeneration; and (3) a "residual stage," which has fixed neurological defects and persistent attacks that are less frequent.

3. Pathobiology

The histological features of RE include cortical inflammation, neuronal loss, and gliosis confined to one cerebral hemisphere. Multilocular inflammation is spreading throughout the hemisphere. Pathogenic signs include microglial and lymphocytic nodules, perivascular cuffing, neuronal death, and neuronophagia. Loss of neural cells, astrogliosis, and cortical cavitation are end-stage symptoms. On the other hand, recent imaging investigations validate long-standing pathology findings suggesting a preference for the fronton-insular region, with the occipital cortex being less frequently affected (6,7). Individuals who experience brain involvement typically have a higher sickness load and are younger. Heterogeneity and diversity in the lesion location, illness course, and degree of pathological abnormalities are crucial indicators of a disease process that affects multiple brain regions at different times. These differences are seen within and across individuals (5,7).

Neuroimmunology: Three types of immunopathological mechanisms are recognized to play a role in central nervous system (CNS) degeneration: antibody-mediated, T-cell cytotoxicity, and microglia-induced degeneration (6,8).

3.1 Antibody-mediated CNS degeneration

It has long been believed that the humoral immune system is untouched by the brain, but new research suggests this may not always be the case. Over the past ten years, it has been evident that circulating antibodies to neuronal surface proteins may be hazardous when they cause several CNS disorders. It has been evident during the past ten years that circulating antibodies to neuronal surface proteins are associated with several potentially fatal CNS disorders. Conversely, GluR3 antibodies were only discovered in a very few number of RE patients treated with plasmapheresis. A subset of individuals with RE had Munc-18-1 in their blood, even though this information was not disclosed. Despite being a signaling pathway neuronal protein required for synaptic vesicle discharge, Munc-18 is not thought to be a major target. Although evolutionarily conserved and an intracellular protein required for synaptic vesicle discharge, Munc-18 is not expected to receive much attention (6,9).

3.2 T-cell cytotoxicity

A significant role for cytotoxic T cells appears to be played in the etiology of Rasmussen's encephalitis. Ten percent or so of the inflammatory T cells are granzyme B-positive, and the majority of these cells are CD8. These granzyme B cells were discovered next to neurons and astrocytes, where the cytotoxic granules are polarized to face the target cell membrane; granzyme B discharge onto neurons has been observed on occasion. Moreover, spectra-typing of the T cells from the brain lesions revealed that these cells developed from distinct precursor T cells that responded to epitopes and were antigenic, indicating specificity for individual brain antigens. Cytotoxic T lymphocytes target neurons and astrocytes, one may assume that each of these cell types expresses an autoantigen. The antigen's identity is yet unknown, though (5–7).

3.3 Microglia-induced neuronal degeneration

One of the neuropathological features of Rasmussen's encephalitis is microglial activation. Although these cells' levels of activation can range between brain regions, they generally follow the stages of development and pattern of T-cell infiltration of cortical damage. Microglia play a role in the onset of seizures in various epileptic conditions through the release of pro-inflammatory cytokines and proteins such as interleukin. Additionally, complement-induced synaptic stripping, which can raise network excitability, is mediated by activated microglia. It is still unknown, though, exactly what pathogenic role microglial cells play in Rasmussen's encephalitis. Rasmussen's encephalitis also causes activation of astrocytes in addition to microglia. The progression of cortical injury is tightly correlated with the pattern of astroglial activity. Thus, astrocytes most likely play a comparable function in the inflammatory response in Rasmussen's encephalitis (6).

3.4 Inflammatory gene expression

To understand more about the composition of the immune response in cases with Rasmussen's encephalitis, the proportions of 86 mRNA transcripts associated with inflammation and Quantitative PCR were used to assess autoimmunity in 12 Rasmussen's encephalitis brains. The analysis demonstrated that greater levels of expression were seen for a selection of seven functionally relevant genes that code for interferon-γ, CCL5, CCL22, CCL23, CXCL9, CXCL10, and Fas ligand when comparing the cortical dysplasia cohort to the Rasmussen's encephalitis cohort. These genes cause activation of helper and inducer, memory, and effector T cells (6,7).

4. Diagnosis

RE is defined by a range of clinical signs and symptoms, none of which are individually diagnostic. Even though EPC is rare, it can occur in other conditions like Alpers syndrome. The diagnostic criteria proposed by Bien et al. include a combination of clinical presentation, EEG findings, MRI characteristics, and histopathological features, as summarized in Table 1 (10,11).

Table 1. RE diagnostic criteria

Part A: Clinical, EEG, and MRI	
Clinical	Focal seizures and deficits in one cerebral hemisphere.
EEG	Significantly lateralized slowing of brain activity and seizures originating from one side
MRI	Pronounced focal cortical atrophy on one side of the brain and at least one of the following: 1. Hyperintensity in gray or white matter on T2/FLAIR (fluid-attenuated inversion recovery) imaging. 2. Atrophy or hyperintensity in the ipsilateral caudate head on T2/FLAIR imaging.
Part B: If not fulfilled Part A	
Clinical	EPC or Progressive* unilateral cortical deficits
MRI	Progressive* and significantly lateralized cortical atrophy
Histopathology	T-cell–dominated encephalitis with activated microglial cells (often forming nodules) and reactive astrogliosis; the presence of numerous parenchymal macrophages, B-cells, plasma cells, or viral inclusion bodies excludes the diagnosis of RE

Progressive*: It indicates that there have been at least two consecutive examinations or studies; italics suggest recommended changes.

5. Recent advancement in treatment (6,9,11)

5.1. Medical management

- High-dose methylprednisolone (MP), IVIg, plasmapheresis, or immunoadsorption: variably effective in seizure control and may slow disease progression temporarily.
- Calcineurin inhibitors (e.g., tacrolimus): shown to slow hemiatrophy progression and reduce cognitive decline but not effective for seizure control.
- Combination therapies (e.g., steroids, IVIg, tacrolimus, mycophenolate mofetil, cyclophosphamide, alemtuzumab, methotrexate, rituximab): mixed short-term success reported in various case studies.
- Adalimumab: reduced seizure frequency by more than 50% in some patients and stabilized neurological decline in a few cases.

5.2. Surgical management by Hemispherectomy and hemispheric disconnection (HD) in RE

- Hemispherectomy and HD are the only established methods to cure RE seizures, with success rates of 70–80%.
- Advances in neuroimaging and neuroendoscopy have improved HD techniques, minimizing risks.
- Common HD techniques:
  - Modified functional hemispherectomy
  - Peri-insular hemispherectomy
  - Parasagittal hemispherectomy
  - Endoscopic-assisted hemispherectomy
- HD requires technical expertise and carries a risk of incomplete disconnection

6. Patents

The patents related to the management of the disease are mentioned in table 2

Table 2. Summarizes an update on patents on RE

S. No.	Patent Number	Title	Year	Status	Ref
1.	EP2490691A1	Use of 1h-quinazoline-2,4-diones	2012-08-29	Withdraw	(12)
2.	WO2011048150A1	Use of 1h-quinazoline-2,4-diones	2011-04-28	Published	(13)
3.	CA 2698831	Use Of A Peptide As A Therapeutic Agent	2010-03-08	Dead	(14)

7. Conclusion

Rasmussen encephalitis (RE) presents challenges in diagnosis and management due to its rarity and progressive nature. Diagnostic criteria include clinical, EEG, MRI, and histopathological features. Recent treatments like high-dose methylprednisolone, IVIg, and surgical interventions show promise but with varying success rates. Adalimumab has demonstrated efficacy in reducing seizure frequency. Surgical methods like hemispherectomy boast success rates of 70–80% but require expertise and carry risks. Ongoing patent activity indicates continued interest in developing therapies. Further research is needed to enhance diagnostic accuracy and treatment effectiveness for RE.

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