SYSTEMATIC REVIEW

Different modalities of the treatment of Rasmussen encephalitis: A systematic review of case reports of a rare disease [version 1; peer review: awaiting peer review]

Rajan Chamlagain, Sangam Shah, Sangharsha Thapa, Bipin Kandel, Roman Dhital, Basanta Sharma Paudel, Sujan Poudel, Angela Ishak, Vinayak Aryal, Pamela Youssef, Kester J. Nedd

1Tribhuvan University, Institute of Medicine, Maharajgunj, 44600, Nepal
2Department of Neurology, Jacobs School of Biomedical Sciences, University of Buffalo, Buffalo, 14203, USA
3Research and Academic Affairs, Larkin Community Hospital, Miami, FL, 31143, USA
4Department of Neurology, Larkin Community Hospital Palm Springs Campus, Hialeah, FL, 33002, USA

First published: 14 Sep 2022, 11:1049
https://doi.org/10.12688/f1000research.124673.1
Latest published: 14 Sep 2022, 11:1049
https://doi.org/10.12688/f1000research.124673.1

Abstract

**Background:** Rasmussen's encephalitis (RE) is a rare chronic neurological disorder that presents with progressive neurological and cognitive deterioration, and intractable seizures that lacks definitive management. We aimed to identify case reports of RE in the literature to assess the treatment based on the symptoms and outcomes after the treatment.

**Methods:** We searched the databases PubMed, Google Scholar, and the Cochrane Library from 1990 to 22nd February 2022 in order to review the case reports that included the treatment options and clinical outcomes of RE. A pre-established protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42021261999).

**Results:** The mean age of onset of seizure was 31.44 and 6.87 years in adult onset RE and children (below 15 years of age) with RE respectively. A total of four (44.44%) out of nine adult patients and 81 (66.39%) out of 122 children underwent surgery. Tacrolimus was used in 17 (13.93%) and steroid therapy was used in 11 (9.01%) of the children.

**Conclusions:** Large scale-controlled trials are needed to study the beneficial effect of tacrolimus, IV Ig, and plasma therapy. Hemispherectomy should be opted as a treatment modality by assessing the impairment of patients' motor or language functions following the treatment procedure.

**Keywords**
Rasmussen encephalitis, tacrolimus, hemispherectomy, systematic review, neurological disorder, treatment
Corresponding author: Sangam Shah (sangam.shah.1997@gmail.com)

Author roles: Chamlagain R: Conceptualization, Data Curation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Shah S: Conceptualization, Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing; Thapa S: Data Curation, Writing – Review & Editing; Kandel B: Methodology, Writing – Review & Editing; Dhital R: Software, Writing – Review & Editing; Sharma Paudel B: Formal Analysis, Writing – Review & Editing; Poudel S: Formal Analysis, Writing – Review & Editing; Ishak A: Investigation, Methodology, Writing – Review & Editing; Aryal V: Validation, Writing – Review & Editing; Youssef P: Supervision, Writing – Review & Editing; J. Nedd K: Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2022 Chamlagain R et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Chamlagain R, Shah S, Thapa S et al. Different modalities of the treatment of Rasmussen encephalitis: A systematic review of case reports of a rare disease [version 1; peer review: awaiting peer review] F1000Research 2022, 11:1049 https://doi.org/10.12688/f1000research.124673.1

First published: 14 Sep 2022, 11:1049 https://doi.org/10.12688/f1000research.124673.1
Introduction

Rasmussen’s encephalitis (RE) is a rare chronic neurological disorder characterized by unilateral inflammation of the cerebral cortex and presents with intractable seizures and progressive neurological and cognitive deterioration. In Germany and the United Kingdom, the incidence of RE is 2.4 cases per 10 million persons and 1.7 cases per million per year, respectively. However, there is no worldwide published statistics on sex, geography, or ethnic predilection. Acutely, patients with RE experience a progressive loss in neurological functions such as hemiparesis, hemianopia, cognitive impairment, and aphasia in the affected hemisphere. Patients also commonly experience intractable unilateral simple partial focal motor seizures, complex partial seizures, or secondary generalized seizures. The diagnosis is usually based on a European consensus panel for Rasmussen’s encephalitis 2005.

The aetiology of RE is still not fully understood. A possible hypothesis was that the disease could be due a possible viral infection, however, this remains to be proven. Antibody-mediated immune response directed towards antigens of brain resident cells is another mechanism hypothesized. Antibodies to the AMPA receptor subunit 3 (GluR3 antibodies) have been suggested as the pathogenesis. They are, however, neither sensitive nor specific to RE. Antibodies directed against non-GluR3 may play a role in the development of RE in some cases. RE has recently been linked to antibodies to the neuronal alpha7 acetylcholine receptor and the presynaptic protein Munc18-1. RE is thought to be an immunological-mediated disease involving both adaptive and innate immune responses which are aided by microglia and astroglia. However, in some case series, dual pathology has been found in patients with RE suffering from focal cortical dysplasia or tuberous sclerosis. The most recent literature has described inflammation in conjunction with localized cortical dysplasia type 2b lesions.

The goal of disease management in RE patients is to reduce the frequency and severity of seizures, and to improve long-term functional outcomes. Seizures are managed by anti-epileptic drugs (AED). Long-term corticosteroids, intravenous immunoglobulins, plasmapheresis, or protein A immunoadsorption; T-cell inactivating medicines, tacrolimus and azathioprine; and surgery (hemispherectomy or hemispherotomy) have all been used to treat people with RE. However, these treatment modalities are used only to alleviate symptoms. There is no definitive cure because of the disease rarity. Although a systematic evaluation of case reports cannot establish a link between definitive therapy and results, it can form a basis for hypothesis formulation in subsequent studies. Our aim in this review was to identify the cases of RE in the literature to assess the treatment based on the symptoms, and outcomes after the treatment.

Methods

This systematic review conforms to standard guidelines and is written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) statement. A pre-established protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42021261999).

Study selection

We searched electronic databases including PubMed, Google Scholar, and The Cochrane Library through 1990 to 22nd February 2022 to review the case reports that included the treatment options and clinical outcomes following the treatment in patients diagnosed with RE. “Rasmussen”, “encephalitis”, “treatment”, and “outcome” were used as keywords to search relevant literature. The keywords were combined with “OR” and “AND” Boolean operators. References of the articles included were also searched manually.

The inclusion criteria for the articles were:

1. Case reports and case series
2. Articles that were available in the English language
3. Articles containing information including gender, age, treatment methods, follow up, outcomes, and complications
4. Articles assessing patient management and outcome
The **exclusion criteria** were:

1. Articles that were not available in English
2. Articles not mentioning the treatment

**Quality assessment**

A modified version of an appraisal tool was used for quality assessment of the included case reports. One author (SS) carried out the assessment and a random sample was cross checked by RC. Any disagreement was resolved with discussion by BSP, RD, and BK. We used three items to assess the quality of case reports: (1) chief complaint, history, treatments, follow up, outcomes were described adequately or not; (2) whether accurate diagnosis was provided; and (3) complication or whether the patient improved was mentioned. Items were graded with ratings noted as yes, partially, or no.

**Data extraction**

Two authors (SS and RC) extracted data on to a Microsoft Excel® 2019 sheet. The data from the included studies were extracted as follows: a) author and year of study; b) number of patients; c) age and gender; d) disease management; e) treatment duration; f) outcomes; and g) complications.

Extracted data was checked by another author (RD) and disagreement was resolved by discussion with other authors (BK and BSP) by consensus. We included all studies where the diagnosis was made by serology or any combination of serology with pathologic findings, and immunostaining.

**Data synthesis and analysis**

Data were summarized using descriptive statistics. We calculated the mean for continuous variables, and frequencies and percentages for dichotomous variables.

**Results**

**Publication characteristics**

The literature search resulted in 732 studies from PubMed, Google Scholar, and the Cochrane Library. After the complete screening process of titles and abstracts 631 studies were excluded. A further five articles were not retrieved because full text was not available and a further 35 were excluded following full-text screening as they failed to fulfil the inclusion criteria. Finally, 39 articles that met the criteria were included in the review. A description of study selection is shown as a flow diagram in Figure 1.

**Quality appraisal**

The selected cases were good to moderate in quality. The included cases had an adequate description of the chief complaint, patient past medical history, laboratory investigations, treatment, follow-up and outcomes. The outcomes of treatment and follow-up were included in all (100%) of the studies. Accurate diagnosis with valid and reliable outcome measures were reported for 74.35% of studies. Complications and symptoms that did not improve were reported in 48.71% of the studies (Table 1).

**Demographic characteristics**

The total number of patients with Rasmussen encephalitis was 142 from 39 studies included in this review. The mean age of onset of seizure was 41.11 and 6.82 years in adult onset RE and children with RE (below 15 years of age) respectively. The male to female ratio was 55:74 among the children while 3:10 among the adult-onset RE.

**Clinical features**

Thirty-six out of 38 studies mentioned the clinical features of RE. In those studies, all the patients had at least one episode of seizure. Hemiparesis and focal neurological deficit were observed among 40–50% of patients. Two patients had double pathology of RE.

**Treatment**

Among thirteen patients who had adult onset RE, three (23.07%) patients were treated with intravenous immunoglobulin (IvIg), one (7.69%) with plasma exchange and two (15.38%) patients with rituximab, two (15.38%) patients were treated with IV mitoxantrone while five (38.46%) patients underwent surgery. Of the five patients who had surgery performed, two patients underwent hemispherectomy while in two others selective cortical resection was performed. The fifth patient...
underwent resection of focal epileptic tissue in the sensory cortex. Fluorodesoxyglucose was used along with IvIg and hemispherectomy for RE due to double pathology.

Tacrolimus and steroid therapy were used in 17 (13.17%) adults and 13 (10.07%) of the children. IvIg was used as a treatment option in 11 (8.52%) of the children. Two (1.55%) of the children were given methylprednisolone, cyclophosphamide, and mycophenolate mofetil. Only one (0.77%) child was treated with alemtuzumab with intrathecal methotrexate and natalizumab. Eighty-five (65.89%) of the children ultimately underwent surgery. Of these, hemispherectomy, craniotomy and hemispherectomy were done in 22, one and 56 children respectively. However, surgery was preferred only when other treatment options did not show clinical improvement.

**Follow up and outcomes**

The patients were followed up for a long duration of time (5.38 years). Patients with adult onset RE had better clinical outcomes. Of the thirteen patients with adult onset RE 12 (92.30%) showed clinical improvement: patients were seizure free, there was improvement in neurological function, verbal memory, and working intelligence. Plasma exchange, IvIg, rituximab, IV mitoxantrone, hemispherectomy all showed better treatment outcomes in terms of reduced seizure frequency and normal neurological function. Despite the follow up of one (7.69%) patient for 1.1 years, she had no clinical improvement due to focal cortical dysplasia (dual pathology involved).
There was no clinical improvement in seven children who underwent surgery (three of them died while four had no clinical improvement). Tacrolimus, steroid therapy, methylprednisolone, cyclophosphamide, mycophenolate mofetil, alemtuzumab with intrathecal methotrexate and natalizumab all showed significant improvement in terms of seizure episodes, verbal intelligence and language. The details of the treatment outcomes are shown in Table 2.

| SN No. | Author and year                  | Adequate description | Accurate diagnosis | Complication or whether the patient improved was mentioned |
|--------|----------------------------------|----------------------|-------------------|----------------------------------------------------------|
| 1      | C.G. Bien et al., 2004           | Partially            | Yes               | Partially                                                |
| 2      | N. Bahi-Buisson et al., 2004     | Partially            | Partially         | Yes                                                      |
| 3      | Yuguang Guan et al., 2014        | Partially            | Yes               | Partially                                                |
| 4      | Vera C. Terra-Bustamante et al., 2005 | Yes                 | Yes               | Yes                                                      |
| 5      | Mary L. Zupanc et al., 1990      | Yes                  | Yes               | Yes                                                      |
| 6      | Manuel Arias et al., 2006        | Yes                  | Yes               | Yes                                                      |
| 7      | Catherine Grosmaître et al., 2013 | Yes                 | Partially         | No                                                       |
| 8      | Rochelle Caplan et al., 1996     | Yes                  | Partially         | No                                                       |
| 9      | Sung-Min Cho et al., 2017        | Yes                  | Partially         | Partially                                                |
| 10     | Zuzana Liba et al., 2017         | Yes                  | Yes               | Partially                                                |
| 11     | Jayaprakash et al., 2002         | Yes                  | Yes               | Yes                                                      |
| 12     | C. Sanfilippo et al., 2015       | Yes                  | Partially         | Partially                                                |
| 13     | A. Stabile et al., 2018          | Yes                  | Yes               | No                                                       |
| 14     | Taissa P.F. Ferrari et al., 2011 | Yes                  | Yes               | Yes                                                      |
| 15     | Danielle A. Nolan et al., 2018   | Yes                  | Yes               | Yes                                                      |
| 16     | Katharina Hohenbichler et al., 2017 | Yes              | Yes               | Partially                                                |
| 17     | Flavio Villani et al., 2014      | Yes                  | Yes               | Yes                                                      |
| 18     | L. Papetti et al., 2011          | Yes                  | Yes               | No                                                       |
| 19     | Kevin Gurcharran et al., 2016    | Yes                  | Partially         | No                                                       |
| 20     | Yuguang Guan et al., 2011        | Yes                  | Yes               | Yes                                                      |
| 21     | Barbara Thilo et al., 2009       | Yes                  | Partially         | Yes                                                      |
| 22     | Zuzana Liba et al., 2015         | Yes                  | Partially         | No                                                       |
| 23     | Bhooma R. Aravamuthan et al., 2015 | Yes             | Partially         | No                                                       |
| 24     | Shalini Narayana et al., 2019    | Yes                  | Yes               | No                                                       |
| 25     | Qun Wang et al., 2017            | Yes                  | Yes               | No                                                       |
| 26     | Marie-Aude Spitz et al., 2014    | Yes                  | Yes               | Yes                                                      |
| 27     | Vijay M. Ravindra et al., 2015   | Yes                  | Yes               | Partially                                                |
| 28     | Stefan Bittner et al., 2013      | Yes                  | Partially         | No                                                       |
| 29     | Christian G. Bien et al., 2013   | Partially            | Yes               | Yes                                                      |
| 30     | Tiziana Granata et al., 2013     | Partially            | Yes               | No                                                       |
| 31     | M. Topçu et al., 1998            | Yes                  | Yes               | No                                                       |
| 32     | Ali Hammed et al., 2021          | Yes                  | Yes               | Yes                                                      |
| 33     | Anteneh M. Feyissa et al., 2021  | Yes                  | Yes               | Yes                                                      |
| 34     | Arnold J. Sansereve et al., 2020 | Yes                  | Yes               | Yes                                                      |
| 35     | Mohammad Bila Mazar et al., 2022 | Yes                 | Yes               | Yes                                                      |
| 36     | Monika Mochol et al., 2021       | Yes                  | Yes               | Yes                                                      |
| 37     | Ramesh Sharanappa Doddaman et al., 2021 | Yes             | Yes               | Yes                                                      |
| 38     | Ricardo Pires Alvin et al., 2020 | Yes                  | Yes               | No                                                       |
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|-----------------|----------------|---------|-----------------|-----------|--------------------|----------|-------------------------------|---------------|
| 1   | C.G. Bien et al., 2004 | 7              | Median age: 11.6 (4 F/3 M) (2 F patients were adult onset RS) | Simple partial seizure in 8 patients, complex partial seizure in 3 patients | Tacrolimus | 22.4 months | Superior outcome of neurologic function and progression rate of cerebral hemiatrophy | No better seizure outcome |
| 2   | N. Bahi-Buisson et al., 2004 | 11             | 6 years (5M, 6F) | Simple partial seizure in 8 patients, complex partial seizure in 3 patients | Steroid therapy | 9±2 years | Five had significant reduction of seizure frequency with disappearance of epilepsia partialis continua, and improved motor function | Six patients had no benefit from steroid therapy and underwent hemispherotomy, two died of unexpected sudden death 5 and 7 years after seizure control |
| 3   | Yuguang Guan et al., 2014 | 20             | 5.71 years (11F, 9M) | Epilepsy was the first manifestation of the condition in all patients | 6 left hemispherectomy and 14 right hemispherectomy | 5.45 years | All of the patients had increases in cognitive abilities after surgery most patients could walk independently | 1 patient with bilateral RE, fine movement of the hands was lost |
| 4   | Vera C. Terra-Bustamante et al., 2009 | 25             | 4.4±2.0 years (13M, 12F) | Epilepsia partialis continua in 24 patients and 1 patient had focal motor seizure | Hemispherectomy | 63.3 months | Eleven patients were completely seizure-free. Twelve patients with mild facial jerks (six patients), sporadic hemigenralized tonic-clonic seizures (three patients), and frequent tonic-clonic seizures continued to experience seizures (three patients). After surgery, deterioration in the mental and linguistic functions was seen in 15 and 12 individuals, respectively | Comparing pre- and post-operative language deficiencies, it was shown that 66.7% of the 12 patients with language disorder did not improve after surgery. Only two patients showed improvement in their cognitive function. |
| 5   | Mary L. Zupanc et al., 1990 | 1              | 7/F | Simple partial seizures which initially consisted of speech arrest, drooling, and burning and aching pain in her right leg | Left partial hemispherectomy followed by functional hemispherectomy | 9 months | Died | Acute cerebral hemorrhage |

Table 2. Characteristics of the included studies.
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|-----------------|----------------|---------|-------------------|-----------|--------------------|----------|-------------------------------|---------------|
| 6   | Manuel Arias et al., 2006 | 1              | 51/M    | Generalized motor seizures, intermittent metallic tinnitus, like a bell ringing | IV polyclonal immunoglobulins (0.4 mg/kg daily for 5 days) twice a month | 15 months | No motor deficit and only brief and very isolated partial visual seizures. Language partially improved. | Right homonymous hemianopsia did not change |
| 7   | Catherine Grosmaître et al., 2013 | 1              | 11/F    | Partial seizures (collapse of her right leg leading to falls) | Left hemispherectomy | 4.1 years | Verbal intelligence, working memory, and language improved. She also became seizure free | |
| 8   | Rochelle Caplan et al., 1996 | 4              | 4/11.7/5/5 F | Complex partial seizures deviation of the eyes and head to the left, tonic extension of the left arm and both legs, and flexion of the right arm/onset of clonic jerking of the left hand and arm following a viral tonsillitis/repeated eye fluttering, grimacing, drooling, sensation of a sore throat, and need to touch her throat/tonic clonic seizures, status epilepticus, coma, and left spastic hemiparesis | Right hemispherectomy | 21/19.3/9.1/17.5 months | Language and formal thought disorder | |
| 9   | Sung-Min Cho et al., 2017 | 1              | 11/M    | Refractory status epilepticus | IV immunoglobulin (IV Ig) (0.5 g/kg) with tacrolimus | 1.5 years | Motor deficit resolved completely | Seizures occurred occasionally |
| 10  | Zuzana Liba et al., 2017 | 1              | 7/M     | Right-sided hemiparesis with refractory epilepticus | IV alemtuzumab (total dose of 0.75 mg/kg for three consecutive days) with intrathecal methotrexate 12 mg for a single dose | At 18 months after the surgery | No functional use of the right hand, hardly walks, and speaks in very simple sentences | Relapse occurred Systemic reaction and hyperpyrexia, |
| 11  | Jayaprakash et al., 2002 | 1              | 4/M     | Tonic clonic seizure with fever | Steroids and IVIG and left hemispherectomy | 3 years | Steroids and IVIG failed but after surgery he ambulated, and speech was normal | Residual hemiplegia |
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|----------------|----------------|---------|-------------------|-----------|------------------|----------|-----------------------------|--------------|
| 12  | Sanfilippo et al., 2015 | 1 | 32/F | Ascending epigastric sensation, chest tightness and paresthesia and weakness of the left part of the body later motor seizure with clonic movement of left side | AED, steroids, and plasma exchange | 18 months | Plasma exchange showed improvement of symptoms | High dose steroids had poor outcome |
| 13  | Stabile et al., 2018 | 2 | 33/38/F | Focal unaware seizures, right-hand EPC, ipsilateral hemiparesis, and aphasia/focal unaware seizures with tonic clonic evolution frequently leading to SE, right hemiparesis | IV mitoxantrone mean dose 10.5 mg/m2 every 2–3 months | 25/24 months | Seizure frequency decreased in both the cases |
| 14  | Taissa P.F. Ferrari et al., 2011 | 1 | 5.5/F | Progressive hemiparesis without epilepsy later developed seizure | Right hemispherectomy | 16 months | Seizure free and able to walk without assistance | Worsening of left hemiparesis |
| 15  | Danielle A. Nolan et al., 2018 | 1 | 9/F | Typical absence seizures, 1 year after diagnosis new-onset frontal headache for one week before suddenly developing left neck twitching. This progressed to involve her left arm and leg, followed by sudden left hemibody loss of sensation | Hemispherectomy | 4 years 3 months | Died | IV immunoglobulin, AED, high dose steroids failed |
| 16  | Katharina Hohenbichler et al., 2017 | 1 | 17/F | Tonic clonic seizures initially two months later, the patient developed motor status epilepticus with continuous jerks of the right hand, clinically corresponding to epilepsia partialis continua (EPC) | Hemispherectomy, IVlg, fluorodesoxyglucose | 1.1 years | No clinical outcomes | Due to focal cortical dysplasia (double pathology) |
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|-----------------|----------------|---------|-------------------|-----------|-------------------|----------|-------------------------------|---------------|
| 17  | Flavio Villani et al., 2014 | 2 | 28/M | EPC with myoclonic jerks involved the tongue and the right face muscles and spreading to right limbs in 6 years | Conservative management: AED regimens such as carbamazepine, valproate, phenytoin, levetiracetam, and clonazepam and different trials with immunomodulatory therapies (high dose and chronic steroids, IVIG, plasmapheresis, and immunoadsorption with A protein). Surgical treatment: Selective cortical resection | 54 months after surgery | Patient was seizure free, reduced AED drugs | Moderate to severe non-fluent language deficit in 1st patient |
|     |                 | 35/F | Sporadic secondary generalized convulsive seizures with focal motor onset (left face and upper limb) | EPC months of the left facial muscles and later involving the oral territory and neck after 16 months | Conservative management: AEDs carbamazepine, levetiracetam, valproate, and benzodiazepine, and high dose and chronic steroids, IV Ig, and plasmapheresis | Surgical treatment: Cortectomy of the right frontal operculum | 31 months | No adjunctive neurologic deficits and no progression of atrophy at MRI were observed after surgery. Patient stable on prednisolone therapy | One secondary generalized seizure a few days after a benzodiazepine dose reduction after 31 months of surgery |
| 18  | L. Papetti et al., 2011 | 1 | 9/F | Episodic left complex partial seizures | IV immunoglobulin | 4 years | Reduction in seizure frequency and improvement of EEG pattern |
| 19  | Kevin Gurcharran et al., 2016 | 1 | 2/F | Subacute onset of progressive right hemiparesis, speech regression and right-side focal seizures | IV immunoglobulin | 12 months | Right sided weakness improved, speech normal |
| 20  | Yuguang Guan et al., 2011 | 1 | 5/M | Seizure involving shaking in his right hand/had three secondarily generalized tonic-clonic seizures (GTCSs) and three complex partial seizures, consisting of blank staring with eye deviation and head turning to the right | Bilateral hemispherectomy | More than a year | No clinical improvement | He cannot talk, walk, or eat without assistance |
| No. | Author and year            | No. of patients | Age/sex | Clinical symptoms                                                                 | Treatment                                                                 | Treatment duration | Outcomes                                                                                   | Symptoms that did not improve                                                                 | Complications                                                                 |
|-----|---------------------------|----------------|---------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 21  | Barbara Thilo et al., 2009 | 1              | 20/F    | Focal clonic and tonic seizures, involving the left arm and the left side of her face, sometimes accompanied by impaired awareness and responsiveness | IV rituximab 375 mg/m²                                                    | 1.5 years          | Patient remained seizure free for 6 months                                                     | Initially treated with immunoadsorption but had no improvement                   |                                                                                 |
| 22  | Zuzana Liba et al., 2015  | 1              | 6/M     | Sudden onset of focal seizures that gradually increased in frequency seizures were characterized by behavioral arrest, eyelid fluttering, and staring, followed by eye deviation upward and left-hand twitching | methylprednisolone 30 mg/kg for three days and seven monthly cycles of cyclophosphamide (750 mg/m²), oral mycophenolate mofetil (MMF, 600 mg/m²) | 6 months           | cognitively intact and making progress in school and have a normal neurologic examination |                                                                                 |                                                                                 |
| 23  | Bhooma R. Aravamuthan et al., 2015 | 1 | 5/F | Simple partial seizures without EPC were accompanied by right arm and face clonic movements. Later, she experienced dysarthria, a right lower face weakness, and cognitive and educational stagnation | Three courses of methylprednisolone (30 mg/kg/mo), 7 courses of cyclophosphamide (750 mg/m²/mo), and mycophenolate mofetil (600 mg/m²/d) | 11 months          | Right facial paralysis has disappeared, seizure frequency has decreased from once daily to once weekly, and academic performance has improved |                                                                                 |                                                                                 |
| 24  | Shalini Narayana et al., 2019 | 1              | 4.11 year/F | Right arm twitching and weakness and right leg weakness/Face and right-sided weakness/Frequent low-amplitude jerks of the right hand, arm, and leg were noted/Muscle strength and fine motor skills was reduced in the right upper and lower extremities and was unable to bear weight on right lower extremity/Mild tightness of heel cord was noted in the right foot/Deep tendon reflexes were brisk in the right side and sustained clonus in the right ankle | Frameless stereotactic MRI-guided left frontal craniotomy and microsurgical functional hemispherectomy | 2 weeks             | After surgical intervention, the patient was seizure free, had stable right-sided hemiparesis, and her speech remained intact and was maintained on oxcarbazepine | Stable right-sided hemiparesis                                                   |                                                                                 |
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|----------------|----------------|---------|-------------------|-----------|-------------------|----------|------------------------------|---------------|
| 25  | Qun Wang et al., 2017 | 1 | 29/F | Convulsions originally manifested as at twitching of the right thumb that extended to the right hand and later to the entire upper limb, reversible hemiplegia, and speech disorders | functional hemispherectomy | 2 years | She was seizure-free, without aggravation of hemiplegia. Verbal and IQ score were improved |  |
| 26  | Marie-Aude Spitz et al., 2014 | 1 | 4/F | Jerks on the right cheek followed by right leg hypertonia and myoclonus causing her to fall and the evolution was marked by bilateralization of seizures, rapidly followed by EPC and an enrichment of seizure types, refractory to antiepileptic drugs | Conservative: AED, corticosteroids, intravenous Immunoglobulins Surgical treatment: Left hemispherectomy | 4 months after surgery | Normal IQ, working memory, distractibility, and moderate reading abilities at school | Right hemiparesis and hemianopsia |
| 27  | Vijay M. Ravindra et al., 2015 | 1 | 12/F | On a neurological examination, the patient had headaches, worsening handwriting, declining academic performance, and social withdrawal over a three-month period. Additionally, the patient had left hemiglissal atrophy, pronator drift of the right upper extremity, and mild weakness of the right hand's intrinsic muscles, grip, and wrist extension | Surgical treatment Craniotomy, Conservative treatment after surgical intervention: Tacrolimus, methylprednisolone, and IVig | 15 months | Her right extremity strength had significantly increased, yet she still has some residual weakness. She no longer had seizures and her cognitive function had not worsened |  |
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|-----------------|-----------------|---------|-------------------|-----------|-------------------|----------|------------------------------|----------------|
| 28  | Stefan Bittner et al., 2013 | 1 | 8/F | Recurrent episodes of EPC as well as other focal seizures and developed a progressive right-sided hemiparesis with partial impairment of language abilities | Conservative management: Dexamethasone and azathioprine, IVIg and a combination therapy of AED (levetiracetam (4 g/day), pregabalin (500 mg/day), and zonisamide (400 mg/day) in, rituximab (1 cycle, 2.3 1,000 mg), IV natalizumab, 300 mg, monthly | 13 months after start of treatment | Reduced seizure frequency | |
| 29  | Christian G. Bien et al., 2013 | 16 | 5.7 years (10 F, 6 M) | Refractory epilepsy (9), Drug-responsive epilepsy (1), Undetermined responsiveness (2), EPC (4) | Tacrolimus (n=9) and IV Ig (n=7) | 6.3 years | Slowed down tissue and function loss and prevent development of intractable epilepsy | Serious event in tacrolimus and No patient with refractory epilepsy became treatment-responsive under immunotherapy |
| 30  | Tiziana Granata et al., 2013 | 16 | 5.8 years (8 M, 8 F) | | | | At the time of the follow-up, all patients but three were seizure-free, ten had discontinued using AEDs, six had significantly reduced their use, and all had improved postural control. Gains in cognitive ability were significantly (p = 0.002) correlated with the severity of the illness | |
| 31  | M. Topçu et al., 1998 | 6 | 7.1 ± 2.2 years (3 M, 3 F) | Left-sided continuous partial epilepsy affecting her face and limbs and a left hemiparesis, seizures manifested as chewing movements, a rightward turn of the head, and difficulty speaking. Right-sided twitching of the face, drooling, deviation of the tongue to the right, and tonic posturing of his right arm were also present, clonic contractions, repeated seizures with tonic-clonic contractions that start in the right hand and move to the right side, epilepsy partialis continua that affects her left side, and persistent left focal motor seizures that impair his face and arm | Surgery | 32.3 ± 17.2 years | In three cases IV Ig therapy yielded temporary and partial improvement in seizure control, Seizures were fully controlled in one patient, in whom surgery was performed 3 months after the seizures first started | |
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|-----------------|-----------------|---------|-------------------|-----------|-------------------|----------|------------------------------|---------------|
| 32  | Ali Hammed et al., 2021 | 2 | 8 year/F | Repeated episodes of clonic seizures including right upper and lower limbs with slurring of speech, cognitive delay, and abnormal gait/right hemiparesis/Muscle power Medical Research Council (MRC) grade 3/exaggerated tendon reflexes on the right side/severe global developmental delay | Immunotherapy either IV Ig followed by methyl prednisolone followed by oral prednisole for 28 days, (surgical intervention being considered) | 4 weeks | Increase in the frequency of seizure to three times a day | No improvement |  |
| 33  | Anteneh M. Feyissa et al., 2021 | 1 | 32 year/F | Headache, fatigue, cognitive dysfunction, focal impaired awareness seizure focal to bilateral tonic-clonic seizures/right homonymous hemianopia | Rituximab monotherapy Neurostimulation therapy | 6 months | Died |  |
| 34  | Arnold J. Sansevere et al., 2020 | 1 | 6 year/M | Focal to bilateral tonic-clonic seizures with visual phenomena, a leftward deviation, and retained consciousness. The nauseated feeling that follows the seizure is followed by limpness. | Conservative therapy: AED like levetiracetam, oxcarbazepine, valproic acid, zonisamide, topiramate, and diazepam, fosphenytoin, IV Ig immunoglobulin, methylprednisolone, rituximab. Surgical treatment: Functional hemispherectomy | 5 years | No evidence of clinical seizures or hemichorea after surgical treatment. After 6 months of hemispherectomy all antiseizure medications were discontinued. Improved impulse control and showed some improvements in many language-based areas with stable neuropsychological function | Struggle with executive function and working memory | Psoriasis in the ears, popliteal fossa, gluteal clefts and umbilicus/right sided non-reactive pupil with gray discoloration of the iris/ chronic anterior uveitis/ cataract and decreased visual acuity |
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|-----------------|----------------|---------|-------------------|-----------|-------------------|----------|-------------------------------|----------------|
| 35  | Mohammad Bilal Mazar et al., 2022 | 1 | 4.5 year/M | Weakness of left side of the body for 7 months/seizure of either left upper limb or lower limb 8-10 episodes per day for 10-15 minutes/aphasic and disoriented in time and space/exaggerated deep tendon reflexes of the left sides/left-sided up-going plantar response | Conservative treatment: Valproic acid, phenytoin, levetiracetam, methylprednisolone | 8-10episodes per day for 10-15 minutes/aphasic and disoriented in time and space/exaggerated deep tendon reflexes of the left sides/left-sided up-going plantar response | Seizure persisted 2-3 times a day but duration is reduced to 15-20 seconds | Aphasia and hemiparesis involving the left side of the body still persistent. |
| 36  | Monika Moholi et al., 2021 | 1 | 45 year/F | At the age of 17, a focal seizure with diminished awareness was followed by a focused to bilateral tonic-clonic seizure. Between the ages of 18 and 26: focal conscious seizures, usually beginning with jerking in the left shoulder, arm, and face, occasionally followed by head rotation/speech impediment, and sporadic focal to bilateral tonic-clonic seizures | Conservative treatment: valproate, fosphenytoin, levetiracetam, clonazepam, and lacosamide. Immunoglobulins and high dose i.v. steroids. Non-invasive trigeminal nerve stimulation, Anakinra Surgical treatment: Resection of focal epileptic tissue in sensory cortex of the right parieto-occipital region/subpial resections in the right motor cortex | 28 years | After injection with Anakinra seizure frequency decreased and after one week seizure stopped. Discontinuation of anakinra after 2 months lead to relapse of seizures. Cognitive function slightly improved | Pneumonia after introduction of anakinra, prone to urinary infections, spastic paralysis of the left arm |
| 37  | Ramesh Sharanappa Doddaman et al., 2021 | 1 | 12 year/F | Seizure onset at the age of 10 years with aura of fear and nausea followed by the tonic deviation of the eyes to the right and blinking with speech arrest/Involuntary tonic-clonic of right upper limb suggestive of EPC/right sided hemiparesis loss of pincer grasp/MRC grade 2/5 and continuous movement of right hand | Conservative treatment: Antiepileptic medications, methylprednisolone Surgical treatment: Left sided endoscopic hemispherectomy | 2 years | Patient is seizure free and the weakness improved from Grade0/5 to 3-4/5 at one year of follow up after surgical treatment. The patient is able to walk independently | Developed hemiplegia immediately after surgery |
| No. | Author and year | No. of patients | Age/sex | Clinical symptoms | Treatment | Treatment duration | Outcomes | Symptoms that did not improve | Complications |
|-----|-----------------|-----------------|---------|-------------------|-----------|--------------------|----------|-----------------------------|---------------|
| 38  | Ricardo Pires Alvim et al., 2020 | 2 | 56 year/M | Clonic movements in the left arm and oculocephalic deviation to the left, with 24 hours of impaired consciousness; a rapid decline in cognitive function over the previous three months, with temporal and spatial disorientation and impaired episodic memory; behavioral issues, including apathy and complex visual hallucinations; bradypsychia and dysarthria; and comprehension of brief commands. Katz Index of Independence in Activities of Daily Living score of 4 out of 6 due to modest left hemiparesis and spasticity. | Carbamazepine 600 mg/d and lamotrigine 150 mg/d; risperidone 1 mg/d; Immunoglobulin (2 g/kg), with cognitive stabilization. | 3 years | Scored 12 on the FAQ and 24 on the MMSE three years later, showing a marginal improvement in functional capacity |  |
| 65  | year/M | At the age of 48, visual hallucinations and partial motor seizures began. Neuropsychiatric symptoms included paranoid delusion, depression, and suicidal thoughts. Loss of complicated daily activities and cognitive decline related to spatial orientation and episodic memory. Simultaneous prosopagnosia and synarthria Bilateral and asymmetric parkinsonism, worse on the left hemibody, and myoclonus on this side were all present on test score 13/30 in addition to mid-left hemiparesis (MRC grade IV/V) and pyramidal symptoms. | AED and corticosteroid pulse therapy. |  |  |

AED: Antiepileptic drug; IVlg: Intravenous immunoglobulin; EPC: epilepsia partialis continua.
Discussion

Rasmussen encephalitis has no reported incidence of male or female predominance, but our results showed that a higher number of females suffered from RE. Seizures were reported in all the patients. To lower the incidence of non-epilepsia partialis continua (EPC) seizures, patients with seizures should be treated with AEDs at any stage of the disease. For periods of status epilepticus, steroid boluses or plasma exchange/Protein A IgG immunoadsorption are indicated. When used early in the disease’s active phase, less than two years following the onset of symptoms and signs, corticosteroids can be beneficial. Late treatment with steroid therapy, on the other hand, results in delayed recovery, recurrence, and hemisphere separation. As a result, new strategies for treating RE are needed, both to control seizures and to prevent the unavoidable neurological degeneration. There is insufficient evidence for the definitive treatment regarding the particular choice of immunotreatment. No specific therapy should be preferred if there are no intractable seizures (e.g. in ‘burned out’ patients).

Steroids, IV Ig, plasma exchange/Protein A IgG immunoadsorption, or tacrolimus appear to be the best options based on current literature. Immunotreated individuals survived more than the control group patients in a randomized controlled trial with tacrolimus and IV Ig; however, neither was superior to the other. Two patients who were on tacrolimus had substantial side effects (febrile infection and asymptomatic Epstein Barr virus (EBV) viremia). Several untreated individuals had persistent epilepsy and later required hemispherectomy, whereas immunotreated patients had no seizures. Similarly, under immunotherapy, no patient with refractory epilepsy became treatment responsive. Another study assessing the therapeutic role of tacrolimus found that patients treated with tacrolimus had a superior outcome with improved neurologic motor functions and rate of progression of cerebral hemiatrophy. However, the outcome with seizures was uneventful. These studies currently show no evidence in favor of one treatment over another, and none of them has been demonstrated to be a viable alternative to surgery in terms of slowing the disease process.

Surgical treatment was done only when other therapies had no better outcomes in most of the studies. Surgical treatment is the preferred method; however, tailored resection, bipolar electrocoagulation on functional cortexes (BEFC), and multilobar resection are not effective for most individuals. Selective resection guided by intracranial monitoring is a good option for adolescent patients. The only successful therapy for obtaining no seizures in RE patients is hemispherectomy and hemispherotomy. In a study by Guan et al., the seizure-free rate was 80%. The majority of the patients were able to walk without support, but their fine hand movements had been lost. However, cognitive evaluation showed that the majority of the patients did not have significant improvement after the surgery in a study by Terra-Bustamante et al.

When the non-dominant hemisphere is afflicted epilepsy is severe, and where hemiparesis has already occurred in older patients hemispherotomy is required. For older people with dominant-side RE, early-stage disease, and modest neurological abnormalities, surgery is a difficult therapeutic choice, thus the decision must be based on adequate follow up, a multidisciplinary approach, and the patient’s and family’s psychological preparation.

Our study had several limitations. The quality of the data in the reports limits our results. The information provided was not consistent or uniform. The higher number of cases with RE could be due to publication bias. Most crucially, case studies and reports are uncontrolled, and while they can suggest possibilities, they can’t prove them. However, doctors should be mindful of the significant number of cases documented in the literature, which show that the pathophysiology of RE may be involved in treatment. While case reports are useful for identifying signals, they are insufficient for statistical inference. As a result, the evidence presented may not be sufficient to recommend regular screening in RE patients.

Conclusions

To investigate the efficacy of non-surgical treatment options such as tacrolimus, IV Ig, and plasma therapy in terms of seizure control and neurologic function preservation, systematic randomized controlled trials are required. Once a patient has been identified with RE, it must be determined whether hemispherectomy would result in a significant impairment of motor or verbal functions. Hemispherectomy should be suggested if no significant worsening is expected.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for ‘Different modalities of the treatment of Rasmussen encephalitis: A systematic review of case reports of a rare disease’, https://doi.org/10.6084/m9.figshare.20477835.v1.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0)
immune-mediated encephalitis. Neurol. Neuroimmunol. Neuroinflammation. 2015; 2: e69. PubMed Abstract | Publisher Full Text

41. Aravamuthan BR, Fernández IS, Zurawski J, et al.: Pediatric anti-HU-associated encephalitis with clinical features of rasmussen encephalitis. Neurol. Neuroimmunol. Neuroinflammation. 2015; 2: e150. PubMed Abstract | Publisher Full Text

42. Narayana S, Embury LM, Shah N, et al.: Noninvasive localization of language cortex in an awake 4-year-old child with rasmussen encephalitis: A case report. Oper Neurosurg. 2020; 18: E175–E180. PubMed Abstract | Publisher Full Text

43. Wang Q, Zhu Z, Wang G, et al.: Functional hemispherectomy for adult rasmussen encephalitis: A case report and literature review. Turk. Neurosurg. 2019; 29: 945–949. PubMed Abstract | Publisher Full Text

44. Spitz MA, Dubois-Teklali F, Vercueil L, et al.: Voltage-gated potassium channels autoantibodies in a child with Rasmussen encephalitis. Neuropediatrics. 2014; 45: 336–340. PubMed Abstract | Publisher Full Text

45. Ravindra VM, Mazur MD, Mohila CA, et al.: Rasmussen encephalitis with dual pathology in a patient without seizures: case report and literature review. Childs Nerv. Syst. 2015; 31: 2165–2171. PubMed Abstract | Publisher Full Text

46. Bittner S, Simon OJ, Göbel K, et al.: Clinical/Scientific Notes. 2013; 395–398.

47. Bien CG, Tiemeier H, Sassen R, et al.: Rasmussen encephalitis: Incidence and course under randomized therapy with tacrolimus or intravenous immunoglobulins. Epilepsia. 2013; 54: 543–550. PubMed Abstract | Publisher Full Text

48. Granata T, Andermann F: Rasmussen encephalitis. Handbook of Clinical Neurology. Elsevier B.V.; 2013; pp 511–519.

49. Topçu M, Turanli G, Aynaci FM, et al.: Rasmussen encephalitis in childhood. Childs Nerv. Syst. 1999; 15: 395–403. PubMed Abstract | Publisher Full Text

50. Hammoud A, Badour M, Bagla S, et al.: Diagnosis and treatment of Rasmussen's encephalitis pose a big challenge: Two case reports and literature review. Ann. Med. Surg. 2021; 68: 102606. PubMed Abstract | Publisher Full Text

51. Feyissa AM, Mohamed AS, Tatum WO, et al.: Brain-responsive neurostimulation in adult-onset rasmussen's encephalitis. Epilepsy Behav. Reports. 2021; 15: 100445. PubMed Abstract | Publisher Full Text

52. Sansevere AJ, Henderson LA, Stredny CM, et al.: Posterior-onset Rasmussen's encephalitis with ipsilateral cerebellar atrophy and uveitis resistant to rituximab. Epilepsy Behav. Reports. 2020; 14: 100360. PubMed Abstract | Publisher Full Text

53. Mazhar MB, Fatima A, Hamid MH: Rasmussen's Encephalitis: A Rare Cause of Intractable Seizures. J. Coll. Physicians Surg. Pak. 2022; 32: 108–110. PubMed Abstract | Publisher Full Text

54. Mocho M, Taubell E, Sveberg L, et al.: Seizure control after late introduction of anakinra in a patient with adult onset Rasmussen's encephalitis. Epilepsy Behav. Reports. 2021; 16: 100462. PubMed Abstract | Publisher Full Text

55. Doddamani RS, Chandra PS, Samala R, et al.: Endoscopic Hemispherotomy for Nonatrophic Rasmussen's Encephalopathy. Neuro. India. 2021; 69: 837–841. PubMed Abstract | Publisher Full Text

56. Alvim RP, Aguilar P, Arnado DK, et al.: Rasmussen encephalitis: an older adult presentation? Dement Neurocogn. 2020; 14: 434–437. PubMed Abstract | Publisher Full Text
The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com