



ELSEVIER

Contents lists available at ScienceDirect

## Pediatric Neurology

journal homepage: [www.elsevier.com/locate/pnu](http://www.elsevier.com/locate/pnu)

## Research Paper

## Role of Early Intravenous Immunoglobulins in Halting Clinical and Radiographic Disease Progression in Rasmussen Encephalitis

Fatima Jaafar, MD <sup>a</sup>, Makram Obeid, MD <sup>b,\*</sup>, Ahmad Beydoun, MD <sup>c,\*\*</sup><sup>a</sup> Division of Child Neurology, Department of Pediatric and Adolescent Medicine, American University of Beirut Medical Center, Beirut, Lebanon<sup>b</sup> Division of Child Neurology, Department of Neurology, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, Indiana<sup>c</sup> Department of Neurology, American University of Beirut Medical Center, Beirut, Lebanon

## ARTICLE INFO

## Article history:

Received 17 August 2022

Accepted 8 May 2023

Available online 15 May 2023

## Keywords:

Rasmussen encephalitis

Intravenous immunoglobulin

Seizures

Volumetric analysis

## ABSTRACT

**Background:** Rasmussen encephalitis (RE) is a rare progressive presumed autoimmune disorder characterized by pharmacoresistant epilepsy and progressive motor and cognitive deterioration. Despite immunomodulation, more than half of the patients with RE ultimately require functional hemispherotomy. In this study, we evaluated the potential beneficial effects of early initiation of immunomodulation in slowing disease progression and preventing the need for surgical interventions.

**Methods:** A retrospective chart review over a 10-year period was conducted at the American University of Beirut Medical Center to identify patients with RE. Data were collected on seizure characteristics, neurological deficits, electroencephalography, brain magnetic resonance imaging results (including volumetric analyses for an objective assessment of radiographic progression), and treatment modalities.

**Results:** Seven patients met the inclusion criteria for RE. All patients received intravenous immunoglobulins (IVIgs) as soon as the diagnosis was entertained. Five patients with only monthly to weekly seizures at the time of IVIG initiation had favorable outcomes without resorting to surgery, along with a relative preservation of the gray matter volumes in the affected cerebral hemispheres. Motor strength was preserved in those patients, and three were seizure free at their last follow-up visit. The two patients who required hemispherotomy were already severely hemiparetic and experiencing daily seizures at the time of IVIG initiation.

**Conclusions:** Our data suggest that the early initiation of IVIG as soon as a diagnosis of RE is suspected, and particularly before the appearance of motor deficits and intractable seizures, can maximize the beneficial effects of immunomodulation in terms of controlling seizures and reducing the rate of cerebral atrophy.

© 2023 Elsevier Inc. All rights reserved.

## Introduction

Rasmussen encephalitis (RE), a rare devastating neurological disease that primarily affects children, is typically characterized by a progressive unihemispheric cortical atrophy clinically associated with focal seizures and gradually worsening unilateral neurological deficits.<sup>1</sup> Although the etiology of RE remains unclear, a presumed autoimmune inflammatory basis is the most accepted hypothesis

based on histopathological hallmarks and variable clinical responses to immunomodulatory therapies.<sup>1,2</sup> This disease, especially when not treated, progresses to pharmacoresistant epilepsy, debilitating neurological deficits, as well as cognitive and behavioral decline. The clinical worsening is accompanied by a prominent electroradiographic progression. Indeed, within months of onset, cortical and subcortical hyperintensities emerge on brain magnetic resonance imaging (MRI) with worsening hemispheric atrophy.<sup>1,3</sup> An increase in the density of epileptiform discharges on the electroencephalography (EEG), particularly contralateral involvement, correlates with worsening seizure severity and cognitive status.<sup>1,4</sup> Because the brain MRI and EEG findings are nonspecific during the initial stages of the disease, an early diagnosis of RE is often challenging.<sup>4</sup>

\* Communications should be addressed to: Makram Obeid MD; Indiana University School of Medicine; Neurosciences Research Building, NB 514G320 W. 15th Street, Indianapolis, IN 46202.

\*\* Dr. Beydoun; Department of Neurology; American University of Beirut Medical Center; P.O. Box 11-0236; Riad El-Solh, Beirut 1107 2020, Lebanon.

E-mail addresses: [makobeid@iu.edu](mailto:makobeid@iu.edu) (M. Obeid), [ab29@aub.edu.lb](mailto:ab29@aub.edu.lb) (A. Beydoun).

The effectiveness of nonsurgical treatments, such as immunomodulation, in controlling seizures and halting the progression of RE may be limited by delays in diagnosis and treatment initiation. Typically, immunomodulation is started relatively late in the course of the disease, after the emergence of confirmatory progressive MRI changes<sup>1,5,6</sup> and evolution of the neurological deficits.<sup>5–7</sup> This delay in treatment initiation may explain why more than 50% of patients with RE ultimately require a functional hemispherotomy to achieve seizure control.<sup>1,3,6,8</sup> At our medical center, immunomodulation with intravenous immunoglobulins (IVIGs) is initiated as soon as RE is suspected, and ideally, before the development of pharmacoresistant epilepsy and severe motor deficits.

In this study, we retrospectively reviewed the treatment and clinical outcomes of patients with RE who were evaluated at the American University of Beirut Medical Center (AUBMC) over the last 10 years. Our aims were to determine whether early initiation of immunomodulatory therapy could lead to adequate seizure control, slow disease progression, and prevent the need for surgery with its inevitable functional consequences. To provide an objective assessment of disease progression, we performed a volumetric analysis of serial MRIs and correlated the results with the clinical features.

## Methods

### Study population

This is a retrospective cohort study of patients diagnosed with RE and treated at the AUBMC from January 2010 to June 2020 and followed for at least two years. To ensure that all eligible patients were included, medical records from a 10-year period (2010 to 2020) were searched using the International Classification of Diseases (ICD) code of encephalitis and the term Rasmussen. These records were then reviewed by two epileptologists to confirm the RE diagnosis.<sup>9</sup> This study was approved by the Institutional Review Board at the AUBMC and classified as a service evaluation involving anonymized analysis of previously acquired data that did not require individual participant consent. Clinical data, EEG, and MRI reports were collected by reviewing scanned medical records or electronic health records, depending on the admission period. Patients with a history of stroke, traumatic brain injury, or uni-hemispheric epileptic syndrome such as Sturge-Weber disease or hemimegalencephaly were excluded.

### Data collection

The data extracted for this study included patient demographics, age at seizure onset, seizure characteristics such as frequency and semiology, the development of *epilepsia partialis continua* (EPC), baseline neurological examination, progression of neurological deficits, cerebrospinal fluid (CSF) studies, and serial EEG and brain MRI results. Hemiparesis was graded as mild for a motor power of 4<sup>+</sup> to 5<sup>-</sup>/5, moderate for a motor power of 3<sup>+</sup> to 4<sup>-</sup>/5, and severe for a motor power of 3 or less. Information was also collected on treatment modalities, such as the types and number of antiseizure medications (ASMs), steroids, ketogenic diet, IVIG, vagus nerve stimulator, and surgical interventions.

### Brain MRI images acquisition and volumetric analyses

Patients who underwent an epilepsy imaging acquisition protocol brain MRI on a 1.5- or 3-T scanner were included for volumetric analysis. The MRI protocol included a three-dimensional volume T1-weighted sequence (1 mm slice thickness) and three-dimensional volume fluid-attenuated inversion recovery

sequence (0.9 or 1 mm slice thickness) of the whole brain with multiplanar reconstruction. In addition, axial and coronal inversion recovery (2 mm slice thickness), axial T2 turbo spin echo, axial T2 fast field echo 4 mm slice thickness), and axial diffusion-weighted images (4 to 5 mm slice thickness) were obtained. Serial MRIs were performed every one to two years or as clinically indicated to longitudinally assess the degree of atrophy. Volumetric analyses of all initial and follow-up brain MRIs acquired with a 3D T1 sequence were performed by using the VolBrain software (<https://www.volbrain.upv.es/>), an automated online brain volumetry system.<sup>10</sup> We used the software dcm2nii (part of the MRICRON software) to convert the T1-weighted images from DICOM to NIFTY format and anonymize them. Whole-brain segmentation was then performed using an automated technique, which separates tissue from CSF by means of thresholding and a series of erosions and dilations.<sup>10</sup> Included in the volumetric analysis are the hemispheric volumes of the gray matter, white matter, and CSF in addition to the volumes of specific subcortical structures. In this study, we focused on the gray matter interhemispheric ratio (GRvol), since it was previously found to be the most sensitive parameter of cerebral atrophy in RE.<sup>11</sup> The GRvol was calculated by dividing the gray matter volume of the affected hemisphere by the gray matter volume of the unaffected hemisphere.<sup>12</sup>

### Treatment protocol

At our center, patients are started on IVIG treatment as soon as the diagnosis of RE is suspected. The dosing regimen consists of an initial dose of 2 g/kg administered over five days, followed by a monthly maintenance dose of 0.4 g/kg. The monthly injection is administered for 18 months following which the interval is progressively extended to every two to four months based on the clinical response. In addition, steroids are administered as an adjuvant treatment during flare-ups of seizure frequency, either in the form of a high-dose intravenous pulse of methylprednisolone (30 mg/kg/day) for four days or as an oral steroid course for variable periods depending on the clinical response. The choice and dosing regimens of ASMs are left to the discretion of the treating physician. Surgical interventions are offered to patients who continue to experience a high seizure burden despite treatment with two or more appropriately selected and dosed ASMs and IVIG administration for at least three months. Surgical candidates include those with hemiparesis, minimal or no fine motor hand movements, and language contralateral to the planned resection if performed after age six years.

## Results

### Patient characteristics

Following a thorough review of our hospital database, we identified seven patients who satisfied the clinical criteria for RE.<sup>9</sup> Table 1 provides a summary of the clinical profile of these patients, which included five males and two females who were followed up for an average of 9.0 years (median: 7.0 years; range = 4.6 to 21.0 years). Two of these patients underwent a modified hemispherotomy (patients 6 and 7), whereas the remaining received medical treatment. The two patients who underwent a modified hemispherotomy fulfilled both parts A and B<sup>9</sup> of the RE clinical criteria (Table 1). Patients 2, 3, and 4 met all five criteria of part A, with Patient 2 also satisfying two of the three criteria of part B. Patients 1 and 5, on the other hand, met only four of five of the part A criteria (lacking unilateral cortical deficits) but satisfied the part B criteria (clinical and MRI).

**TABLE 1.**  
Clinical Characteristics of the Study Population

Cases	Gender	Age at Seizure Onset (Years)	Seizure Semiology	Baseline Monthly Seizure Frequency	Number of Baseline ASMs	Baseline Deficits	Fulfill RE Diagnostic Criteria	
							Part A	Part B
<b>Medicals</b>								
1	F	4.0	FAM and FIA	20	3	No motor deficits; ADHD	No	Yes
2	M	5.0	FAM and FIA	1	5	Moderate hemiparesis	Yes	Yes
3	F	6.0	FAM and FIA	4	1	Mild hemiparesis	Yes	No
4	M	9.0	FAM	4	3	Deficits in fine motor movements of hand	Yes	No
5	M	35.0	FAM and FIA	3	2	None	No	Yes
<b>Surgical</b>								
6	M	5.5	FAM	>100	6	Severe hemiparesis	Yes	Yes
7	M	6.5	FAM	>100	5	Severe hemiparesis	Yes	Yes

**Abbreviations:**

ADHD = Attention-deficit/hyperactivity disorder

ASMs = Antiseizure medications

F = Female

FAM = Focal aware motor

FIA = Focal impaired awareness

M = Male

RE = Rasmussen encephalitis

Patients 1 to 5 were medically treated. Patients 6 and 7 underwent functional hemispherotomy. Baseline monthly seizure frequency refers to the three-month period before initiating intravenous immunoglobulins.

Seizures were the presenting clinical manifestation in all patients. Seizure onset occurred in early childhood in six of the patients (mean: 6.0 years; range: 4.0 to 9.0 years), except for one patient who developed adult-onset RE with a seizure onset at age 35.0 years. All patients presented with focal aware motor seizures, and four of them also experienced focal impaired awareness seizures (Table 1). At the time of their initial evaluation at AUBMC, five patients experienced between one and 20 monthly seizures while maintained on one to five ASMs, whereas two were experiencing multiple daily focal aware motor seizures despite being treated with five to six ASMs (Table 1). On examination, a severe hemiparesis was documented in two patients, moderate hemiparesis in one, and mild hemiparesis in another. Three patients had normal motor power on examination, although one of them had mild deficits with fine motor movements of one hand (Table 1).

Focal epileptiform activity confined to one hemisphere with or without associated ipsilateral slowing was seen on the EEG of all patients upon presentation. The brain MRI at presentation revealed variable degrees of unihemispheric cortical atrophy in all patients, predominantly in the perisylvian region, associated with increased fluid-attenuated inversion recovery signal in most patients. The left hemisphere was affected in three patients, whereas the right hemisphere was affected in four. CSF studies were performed in four patients and were negative for viral etiologies, as well as *N-methyl-D-ASPARTATE* and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-GluR3) encephalitis.

*Effect of immunotherapy on seizure control*

The timing and response to immunotherapy in each patient are summarized in Table 2. All patients received IVIG without any adverse events noted. The mean duration of seizures before IVIG initiation was 1.9 years (median: 1.4 years; range: 2 months to 5.8 years) except for the patient with adult-onset RE who had seizures for 16 years before starting IVIG treatment. At the time of their initial evaluation at our medical center, two of the seven patients were already initiated on IVIG. The mean duration from the initial evaluation until IVIG initiation was 0.8 month (range: 0 to 2 months) except for the patient with adult-onset RE who received

IVIG seven years after his initial evaluation at AUBMC (Table 2). The five patients with weekly to monthly seizures at the time of IVIG initiation had favorable outcomes without requiring surgery. These patients received IVIG treatment until their last follow-up, for an average duration of 5.1 years (range: 3.0 to 10.3 years). Only one patient (Patient 1) required intravenous methylprednisolone to control seizure flare-up and was treated for a total of three steroid courses throughout his follow-up period. On the other hand, the two patients who underwent surgery had severe daily disabling focal motor seizures and severe hemiparesis at the time of IVIG initiation. These daily intractable seizures persisted despite IVIG administration and only remitted following a hemispherotomy (Table 2).

Of the five patients who did not require surgery, three were seizure free at their last follow-up visit, while being maintained on the same number of ASMs received before IVIG initiation (Table 2). The seizure frequency in one patient remained similar to his baseline despite a reduction in the number of ASMs from five to three. The final patient had an increase in his monthly seizure frequency but experienced an improvement in seizure severity. The focal impaired awareness seizures remitted in that patient, although he continued to experience brief daily focal aware motor seizures that did not significantly affect his quality of life (Table 2). None of these five patients experienced EPC after starting IVIG treatment.

*Effect of immunotherapy on neurological and cognitive outcomes*

The neurological and cognitive status of the five patients who did not undergo surgery remained mostly stable throughout their follow-up. The two patients with normal motor power at baseline remained without motor deficits. The patient with deficits in fine motor movements improved, whereas the motor power of the patient with mild hemiparesis remained stable. The patient with a moderate hemiparesis at baseline experienced a slight worsening of his deficits and developed a learning disability but maintained gross motor ability in his upper extremity and independent ambulation (Table 2). One of the two patients who underwent a hemispherotomy had a mild worsening of his hemiparesis but

**TABLE 2.**  
Summary Table of the IVIG treatment and its effectiveness

Cases	Age at Seizure Onset (Years)	Age at First Visit to AUBMC (Years)	Age at IVIG Initiation (Years)	Average Monthly Seizure Frequency During 3 Months Before Last F/U	Cumulative Months of Seizure Freedom in Months (Longest Seizure-Free Period)	Number of ASM at Last F/U	Spikes in Unaffected Hemisphere	Deficits at Last F/U Compared With Baseline	Duration of F/U (Years)
Medical									
1	4.0	5.5	5.6	Seizure-free	6 (4)	3	No	Unchanged	4.6
2	5.0	6.0	6.2	1	2 (1)	3	No	Mild progression of motor deficits; LD	5.0
3	6.0	7.0	6.3	>100 FAM No FIAS	12 (9)	4	No	Unchanged	10.6
4	9.0	14.8	14.8	Seizure-free	20 (12)	3	No	Improved to normal motor	9.0
5	35.0	44.0	51	Seizure-free	48 (36)	2	No	Unchanged	21.0
Surgical									
6	5.5	6.0	5.7	Seizure-free since the surgery	None until surgery	1	No	Stable hemiparesis; hemianopia; depression	7.0
7	6.5	8.9	8.9	Seizure-free since the surgery	None until surgery	1	No	Mild worsening of hemiparesis; hemianopia; depression; LD	6.0

**Abbreviations:**

ASMs = Antiseizure medications

AUBMC = American University of Beirut Medical Center

F/U = Follow-up

FAM = Focal aware motor

FIA = Focal Impaired awareness

IVIG = Intravenous immunoglobulin

LD = Learning difficulties

Patients 1 to 5 were only treated medically. Patients 6 and 7 underwent hemispherotomy.

maintained ambulation, whereas the motor deficit remained stable in the other. Both those patients experienced depressive symptoms postoperatively and one developed a decline in language function (Table 2).

*Effect of immunotherapy on volumetric analyses of brain MRIs*

Quantitative volumetric analyses were performed on the brain MRIs of five of the seven patients. The other two patients (one of whom underwent a hemispherotomy) had poor-quality studies without 3D T1 magnetic resonance acquisitions and were unable to repeat the imaging studies due to financial constraints.

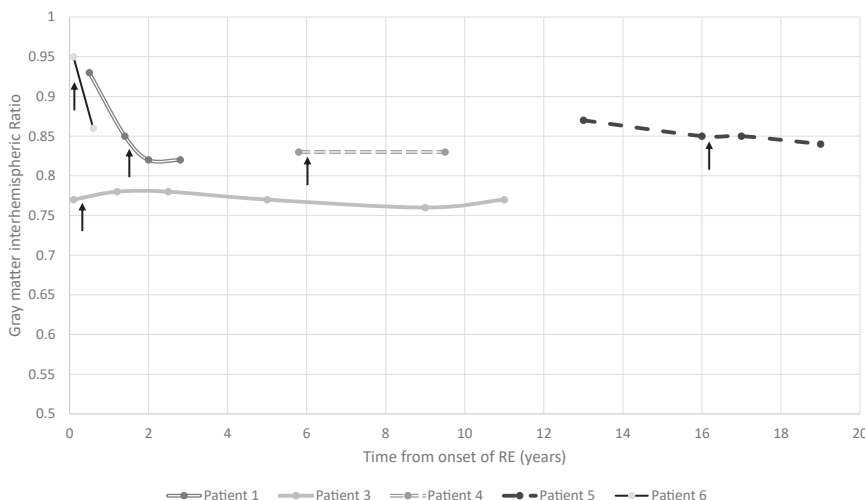
The GRvol on the initial MRI of the four medically treated patients (Patients 1, 3, 4, and 5) ranged between 0.77 and 0.93 (Fig). Following initiation of IVIG treatment (indicated by arrows in Fig), the serial MRIs obtained on those four patients showed either stabilization or mild worsening of the cerebral atrophy. The GRvol in two of those patients (Patients 3 and 4) remained stable at 0.77 and 0.83, with time intervals of 10.6 years and 3.7 years, respectively, between the latest MRI obtained pre-IVIG administration and the latest one acquired post-IVIG (Fig). The GRvol dropped from 0.85 to 0.82 in Patient 1 after a time interval of 1.3 years and from 0.85 to 0.84 in Patient 5 after 3.0 years (Fig).

**Discussion**

In this study, the relatively early initiation of immunomodulatory therapies resulted in favorable outcomes and obviated surgery in five of seven patients with RE who fulfilled the European Consensus Diagnostic Criteria along their clinical course. Our data suggest that initiation of IVIG treatment as soon as a diagnosis of RE is suspected, ideally in the prodromal or early acute stages, and specifically before the appearance of severe motor deficits and intractable seizures, may be effective in maintaining an acceptable

level of seizure control and in halting the progressive neurological, cognitive, and radiologic deteriorations.

Previous studies evaluating the efficacy of IVIG in RE consisted of small series or case reports that reported initial efficacy rates ranging from 23% to 56%, although most patients eventually required surgery.<sup>3,6,13-16</sup> For instance, a study reported the outcomes of 13 patients diagnosed with RE and who received intermittent IVIG therapy with an average lag time of four years since symptom onset.<sup>16</sup> None of the patients achieved seizure freedom, 23% experienced at least 50% improvement in seizure frequency, and 62% had worsening of their motor function.<sup>16</sup> Another study evaluated the seizure outcome of 25 patients with RE who intermittently received a combination of steroids and IVIG for six to 24 months.<sup>6</sup> Of these patients, 14 experienced a transient reduction in seizure frequency, but the majority eventually had to undergo a hemispherotomy. It is worth noting that at the time of starting immunomodulatory treatment, most of these patients were already suffering from EPC and hemiparesis.<sup>6</sup> The few studies that reported on the treatment response according to the timing of IVIG therapy with respect to onset of symptoms are summarized in Table 3. In our cohort of seven patients with a mean follow-up of nine years since onset of symptoms, only two required surgeries whereas the others either achieved seizure freedom or experienced brief focal motor aware seizures. Among the five patients who received medical treatment, the administration of IVIG not only helped control seizures but also prevented the development of progressive motor paresis and stabilized the degree of hemispheric atrophy in longitudinal brain MRIs. We attribute the high success rate in our patient cohort to the prompt administration of IVIG treatment. Our patients began treatment with a mean lag time of 1.9 years since symptoms onset and less than one month after their initial evaluation at our medical center. The severity of hemiparesis and frequency of focal seizures at the start of IVIG treatment distinguished patients who responded to medical therapy in our study from those who required surgery. The two patients who



**Figure.** Gray matter volumetric analysis of the initial and serial brain MRIs in response to IVIG initiation. Patients 1, 3, 4, and 5 were medically treated. Patient 6 underwent hemispherotomy. Arrows represent the time at which IVIG was initiated. IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging.

underwent hemispherotomy had severe hemiparesis and innumerable daily seizures at the time of surgery, despite early IVIG treatment initiation within three months of seizure onset in one patient. These findings are consistent with the results of a randomized study that showed that patients without intractable seizures and with mild or no motor deficits at the time of immunotherapy initiation were most likely to benefit in terms of seizure control and prevention of progressive motor weakness.<sup>5</sup> Conversely, none of the patients with pharmacoresistant epilepsy or severe hemiparesis at the time of immunotherapy initiation improved.<sup>5</sup> The unpredictable progression of symptoms in our patients supports the substantial variability in the severity of the clinical course in patients with RE, with some having a fulminant course and rapid decline despite early treatment with immunomodulatory drugs.<sup>6</sup> For such patients, the response to IVIG should be assessed quickly and those with a positive benefit-risk ratio should be referred for a hemispherotomy.<sup>13</sup> Although the two patients who underwent a hemispherotomy achieved seizure freedom postoperatively, they also developed an expected permanent hemiparesis and hemianopia.<sup>17</sup> In addition, both patients developed depressive symptoms and one patient acquired learning difficulties following the resection. On the other hand, of the five patients who did not require surgery, three were seizure-free and

two had acceptable seizure control at the last follow-up, with their cognitive and motor functions relatively preserved. The most favorable seizure outcomes were observed in those with no or only mild motor deficits at the time of IVIG initiation (Patients 1, 4, and 5), which again highlights the importance of early treatment. Besides seizure freedom, these three patients had a normal motor examination at the last follow-up, no emergence of contralateral EEG abnormalities, and stable serial MRIs, including GRvol.

The diagnosis of RE can be challenging, particularly in its early stage. The detection of a slight hemispheric atrophy can escape visual detection, especially when evaluating images obtained on a nonepilepsy protocol brain MRI.<sup>4</sup> Our results support the value of obtaining thin cuts epilepsy protocol MRI with a 3D T1 sequence and to perform volumetric analyses since it is more sensitive than visual inspection in detecting subtle hemispheric asymmetries.<sup>11</sup> The volumetric analyses can therefore be helpful in expediting the diagnosis and can be used to monitor the disease course and treatment effectiveness.<sup>18</sup> Serial brain MRIs with 3D T1 sequences were available for four of the five patients who did not require surgery. In those patients, the GRvol stabilized or slightly progressed following initiation of IVIG treatment. Interestingly, our study found that the severity of gray matter atrophy at the time of IVIG initiation was not a predictor of response to treatment. Indeed,

**TABLE 3.** Summary Table of Studies That Reported Treatment Response According to Timing of IVIG Therapy With Respect to Onset of Symptoms

Studies	No. of Patients	Time Interval Between Onset of Symptoms and Start of IVIG	Treatment Effect on Seizure Frequency	Treatment Effect on Motor and Cognitive Functions
Granata et al. <sup>14</sup>	8	1.5 ± 1.3 years	3/8: 50%–75 % improvement	1/8: major improvement; 2/8: minor improvement
Takahashi et al. <sup>16</sup>	13	4 ± 5.7 years	23%: >50% improvement None were seizure-free	45%: cognitive stabilization 15%: motor improvement; 62%: motor worsening
Hoffman et al. <sup>3</sup>	8	5.4 years	3/8: transient improvement	NA
Castellano et al. <sup>15</sup>	3	4–11 years	1/3: improvement	1/3: cognitive improvement
Current study	7	1.9 ± 1.7 years (excluding the adult-onset RE)	3/7: seizure-free 2/7: improvement	4/7: stable motor function 1/7: improvement in motor function 2/7: minor motor worsening 5/7: stable cognitive function 2/7: learning difficulties

Abbreviations:  
IVIG = Intravenous immunoglobulin  
NA = Not available  
RE = Rasmussen encephalitis

the GRvol of patients who responded to IVIG treatment ranged between 0.77 and 0.93 at treatment onset, whereas the child who rapidly deteriorated and underwent a hemispherotomy had a GRvol above 0.9 at treatment initiation.

Previous studies have indicated that corticosteroids are highly effective in controlling seizures and in mitigating neurological deterioration.<sup>1,7,16</sup> However, their long-term efficacy remains unconfirmed, largely due to their significant side effect profile limiting long-term use. At our center, we use IVIG as an immunomodulator and administer steroids during seizure flare-ups.

The exact mechanisms by which IVIG exerts its immunomodulatory effects in RE remain incompletely understood. However, several potential mechanisms that may interfere with the underlying pathophysiology of the disease have been proposed. Specifically, IVIG may affect the function of natural killer cells and T lymphocytes, reduce autoantibody levels in the blood saturate Fc-gamma receptors on immune cells, neutralize superantigen, inhibit autoantibodies and cytokines, and inhibit the complement cascade.<sup>19–22</sup> Early administration of IVIG is crucial for optimal treatment results, as the autoimmune response in RE is self-perpetuating and becomes more intense as more neurons are destroyed.<sup>1</sup> Early intervention with IVIG can therefore help minimize brain damage by dampening the immune response. Although other immunomodulatory therapies, such as tacrolimus,<sup>5</sup> mycophenolate mofetil,<sup>23</sup> rituximab, natalizumab, alemtuzumab, and adalimumab,<sup>2,22</sup> have been administered with variable success in RE, their optimal use and timing of initiation require further research.

In summary, our study, although being retrospective, provides preliminary support for the beneficial effects of early IVIG initiation in patients with RE; this is especially true for those who have not yet developed significant motor deficits or worsening of seizure severity. For these patients, this immunomodulatory treatment can halt the progression of the disease, improve seizure control, and reduce the rate of cerebral atrophy. In addition, our study highlights the need to supplement traditional MRI with volumetric brain analyses for a more precise evaluation of disease progression, which could aid in diagnosing the disease at an earlier stage.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgments

We thank Dr. Mhd Khalil Tamragha for assisting with the literature review.

#### References

1. Varadkar S, Bien CG, Kruse CA, et al. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. *Lancet Neurol.* 2014;13:195–205.
2. Orsini A, Foiadelli T, Carli N, et al. Rasmussen's encephalitis: from immune pathogenesis towards targeted-therapy. *Seizure.* 2020;81:76–83.
3. Hoffman CE, Ochi A, Snead 3rd OC, et al. Rasmussen's encephalitis: advances in management and patient outcomes. *Childs Nerv Syst.* 2016;32:629–640.
4. Cay-Martinez KC, Hickman RA, McKhann li GM, Provenzano FA, Sands TT. Rasmussen encephalitis: an update. *Semin Neurol.* 2020;40:201–210.
5. 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.
6. Caraballo RH, Fortini S, Cersósimo R, et al. Rasmussen syndrome: an argentinean experience in 32 patients. *Seizure.* 2013;22:360–367.
7. Bahi-Buisson N, Villanueva V, Bulteau C, et al. Long term response to steroid therapy in Rasmussen encephalitis. *Seizure.* 2007;16:485–492.
8. Obeid M, Wyllie E, Rahi AC, Mikati MA. Approach to pediatric epilepsy surgery: state of the art, part II: approach to specific epilepsy syndromes and etiologies. *Eur J Paediatr Neurol.* 2009;13:115–127.
9. Bien CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain.* 2005;128:454–471.
10. Manjón JV, Coupé P. volBrain: an online MRI brain volumetry system. *Front Neuroinform.* 2016;10:30.
11. Wagner J, Schoene-Bake JC, Bien CG, Urbach H, Elger CE, Weber B. Automated 3D MRI volumetry reveals regional atrophy differences in Rasmussen encephalitis. *Epilepsia.* 2012;53:613–621.
12. Pellegrin S, Baldeweg T, Pujar S, et al. Immunomodulation with azathioprine therapy in Rasmussen syndrome: a multimodal evaluation. *Neurology.* 2021;96:e267–e279.
13. Lagarde S, Boucraut J, Bartolomei F. Medical treatment of Rasmussen's encephalitis: a systematic review. *Rev Neurol (Paris).* 2022;178:675–691.
14. Granata T, Fusco L, Gobbi G, et al. Experience with immunomodulatory treatments in Rasmussen's encephalitis. *Neurology.* 2003;61:1807–1810.
15. Castellano JF, Meyer JA, Lado FA. A case series of adult-onset Rasmussen's encephalitis: diagnostic and therapeutic challenges. *Front Neurol.* 2017;8:564.
16. Takahashi Y, Yamazaki E, Mine J, et al. Immunomodulatory therapy versus surgery for Rasmussen syndrome in early childhood. *Brain Dev.* 2013;35:778–785.
17. Guan Y, Chen S, Liu C, et al. Timing and type of hemispherectomy for Rasmussen's encephalitis: analysis of 45 patients. *Epilepsy Res.* 2017;132:109–115.
18. Wang ZI, Krishnan B, Shattuck DW, et al. Automated MRI volumetric analysis in patients with Rasmussen syndrome. *AJNR Am J Neuroradiol.* 2016;37:2348–2355.
19. McAlpine SM, Roberts SE, Heath JJ, et al. High dose intravenous IgG therapy modulates multiple NK cell and T cell functions in patients with immune dysregulation. *Front Immunol.* 2021;12, 660506.
20. Darlington PJ, Podjaski C, Horn KE, et al. Innate immune-mediated neuronal injury consequent to loss of astrocytes. *J Neuropathol Exp Neurol.* 2008;67:590–599.
21. Owens GC, Garcia AJ, Mochizuki AY, et al. Evidence for innate and adaptive immune responses in a cohort of intractable pediatric epilepsy surgery patients. *Front Immunol.* 2019;10:121.
22. Liba Z, Vaskova M, Zamecnik J, et al. An immunotherapy effect analysis in Rasmussen encephalitis. *BMC Neurol.* 2020;20:359.
23. Liba Z, Muthaffar O, Tang J, et al. Rasmussen encephalitis: response to early immunotherapy in a case of immune-mediated encephalitis. *Neurol Neuroimmunol Neuroinflamm.* 2015;2:e69.