



Rituximab in Rasmussen's encephalitis: A single center experience and review of the literature



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ABSTRACT

Rasmussen's encephalitis (RE) is a rare chronic inflammatory disease of the brain resulting in unilateral hemispheric atrophy with drug-resistant focal epilepsy associated with a variable degree of progressive hemiparesis and cognitive decline. The precise etiology of RE is unknown but presumed to have a neuroinflammatory pathobiological basis. Only surgery halts progression of the disease, but may occur at the expense of a fixed but otherwise inevitable neurological deficit. Therefore, the question of medical management is an important consideration. Reports of rituximab use in patients with RE were presented at the American Epilepsy Society annual meeting in 2008. Good published evidence for its usage has been very slow to emerge since then. However, rituximab continues to be listed in discussions of treatment options for patients with RE, though other monoclonal antibodies have since been used with comparable outcomes.

We describe a series of nine patients including two with adult-onset RE. Rituximab was used early in the disease course (range 1–108 months; mean 32 months).

Of nine patients with RE, there was significant benefit in their seizure burden with rituximab. Seizure freedom occurred in 3 patients. Epilepsia partialis continua (EPC) was present in 4/9 and no focal motor deficit noted in 4/9. No progression of a neurological deficit was present in 2/9 and evidence of progression with neuroimaging was terminated with rituximab in 5/9 supporting early use of rituximab in patients with RE.

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Introduction

Rasmussen's encephalitis (RE) was first described by Theodore Rasmussen in 1958 as a focal encephalitis characterized by epilepsy partialis continua (EPC) with or without other forms of focal-onset seizures, and progressive unilateral neurological deficits and MRI evidence depicting contralateral hemispheric atrophy [1,2]. RE is divided into three stages, the prodromal stage characterized by non-specific symptoms, infrequent seizures and mild hemiparesis that is followed by frequent seizures, often associated

with epilepsy partialis continua (EPC). During the second stage there is progressive hemiparesis, hemianopia, cognitive deterioration, and aphasia (when the dominant hemisphere is affected). In the last stage, permanent and stabilization of neurological deficits and ongoing seizures occur as a residual of the active phase [3–7]. RE is usually a unihemispheric disease, but on rare occasion it may spread to the contralateral hemisphere. It is thought to have an autoimmune cause although antibodies that are specific for the disease are not yet identified [1–5].

The treatment of RE involves treating seizures and EPC as well as preventing disease progression. The only known effective treatment for this devastating disease is functional hemispherotomy, however in the absence of neurological deficits, the timing of surgery may be difficult and subject to the degree of disability

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[5]. In the early stages of the disease process, immunotherapy is used to “arrest” the progression. This includes, intravenous (IV) methylprednisolone, IV immunoglobulin, plasma exchange, and tacrolimus [8–10]. Rituximab is a chimeric mouse-human monoclonal anti-CD20 antibody. It has direct effects on B cells and has been used in less than twenty patients with RE albeit with promising results for some patients [11–19]. Reports of the use of rituximab were presented at the American Epilepsy Society annual meeting in 2008 [18]. Published evidence of safety and efficacy has been slow to emerge since then. However, rituximab continues to be listed in the discussion of treatment options for patients with RE, though other monoclonal antibodies have also been used [10]. It is thus important to consider the potential efficacy of rituximab in limiting disease progression as it is subject to ongoing investigation.

Material and methods

We performed a retrospective chart review of patients with RE followed between 2015 and 2020 at Bajaj Allianz Comprehensive Epilepsy care center at the Deenanath Mangeshkar Hospital in Pune, India. The center is a tertiary epilepsy care center in India, with specific expertise in management of complex epilepsies including epilepsy surgery. The inclusion criteria for this study were: 1) a consensus diagnosis of definite RE by a team of neurologists using previously accepted diagnostic criteria, [2,5] 2) received rituximab, and 3) a minimum follow-up of one year from treatment. The exclusion criteria were: 1) bilateral disease, 2) those who underwent previous surgery, 3) CNS vasculitis, 4) infectious diseases and other immune mediated encephalopathies (such as anti-N-methyl-D-aspartate (NMDA) receptor antibody encephalitis), and 5) metabolic or degenerative progressive neurological diseases. Data were collected from medical records, including clinical data, neuropsychological evaluations, histopathology, and neuroimaging reports.

Indications for starting treatment with rituximab and dose

Patients with continuous EPC, frequent seizures, and recurrent episodes of status epilepticus, and those with minimal or no motor deficit, or RE involving the dominant hemisphere and those who were ineligible for resective surgery received rituximab. Prior to the first rituximab infusion, all patients were screened for hepatitis A, B and C. Chest X rays were performed to exclude pulmonary tuberculosis. Baseline complete blood counts, liver function tests, C-reactive protein, and urine analysis were performed. Rituximab was not administered in the presence of active infection, a previous allergy to rituximab and during pregnancy. All patients who received rituximab were premedicated with IV methylprednisolone, chlorphenamine and oral paracetamol. Rituximab infusion was prepared with 0.9% sodium chloride to make a final concentration of 2 mg/ml. Infusions were delivered at a rate of 25 mg/hour. This rate was flexible and was able to be increased by increments of 25 mg/hour every 30 mins to a maximum of 200 mg/hour as tolerated. During infusion, the patient was monitored for infusion reactions reflected by hypotension, bronchospasm, skin rash, allergic reactions, headache, abdominal pain and conjunctivitis. The dose of rituximab used was 375 mg/m² body surface area weekly for 4 weeks at induction followed by single dose every six months. The endpoints of the study were to find the usefulness of rituximab in controlling seizures, control of EPC, prevention of progression or reversal of motor deficits, as well as the impact on MRI lesions.

Results

Demographic and features

There were seventeen patients with RE during this period, out of which nine patients, (six females and three males) received rituximab and were included in the study. Seven patients satisfied part B of the diagnostic criteria for RE and two patients satisfied part A. The age at the time of evaluation varied from 9 to 33 years (mean 15.7 years). The age at the onset of seizures ranged from 8 to 24 years (mean 12.2 years). Two patients had adult onset RE (24 years of age) and seven patients had childhood onset RE (8–11 years of age). Four patients had focal motor seizures without impaired awareness and five had focal motor seizures with impaired awareness. Seven patients had EPC. These episodes developed one month to 96 months after seizure onset with a mean of 24 months. EPC that developed earlier in childhood with RE (mean 9.5 months) was compared to adult-onset RE. (Table 1) EPC involved the face in one patient, face and tongue in one, and limbs in five patients. Three patients had mild hemiparesis while six did not have any focal neurological deficits. Seven patients had the left hemisphere involved and two had right RE. The duration of epilepsy ranged from 1 month to 108 months (mean 22 months) at the time of evaluation. The number of anti-seizure medications ranged from 3 to 6 drugs. Carbamazepine (10–20 mg/kg/day) was most frequently used followed by, levetiracetam (15–50 mg/kg/day) and clobazam (0.5–2 mg/kg/day, maximum 30 mg/day).

Electrophysiological data

Interictal epileptiform discharges (IEDs) were noted on the side of hemispheric involvement in 7/9 patients and were bilateral in two patients. IEDs were predominantly located in the ipsilateral frontotemporal or frontocentral region. In two patients, contralateral frontal and temporal IEDs were present. Interictal unihemispheric background slowing was present in four patients. Prolonged video-EEG monitoring was done in all patients. Seizure onset arose from the affected hemisphere (lateralizing) in eight individuals and a diffuse onset was present in one. The ictal onset was frontocentral 2–3 Hz delta evolving to 12–15 Hz fast activity in three patients, frontocentral or frontotemporal 4–6 Hz theta in three patients, frontocentral 14–16 Hz rhythm in two patients and diffuse fast activity in one patient.

Neuroimaging findings and treatment

MRI showed hemispheric atrophy in four and cortical or subcortical hyperintensity in five patients. The hyperintensity was frontal paramedian in two, insular in two and insular and temporal in one (Figs. 1 and 2). The timing of MRI was variable, ranging from 1 month to 3 years into the illness, the mean being 6 months. All patients received IV immunoglobulin (2 g/kg distributed over five consecutive days) and methylprednisolone (20–30 mg/kg/day for five consecutive days) during acute phase as well as rituximab. No other immunomodulatory drug was used other than rituximab. The time interval between onset of seizures and receiving rituximab ranged from 1 month to 108 months (mean 32 months). All patients received rituximab within 1 month to 24 month (mean 12.8 months) of illness, except two who received at 96 and 108-months. The time interval between onset of EPC and receiving rituximab ranged from 2 weeks to 96 months (mean 18 months). No patient had any adverse events related to rituximab infusion or long-term therapy. The follow up duration ranged from 12 months to 48 months (mean 22 months).

Table 1
Clinical, demographic features of patients.

Case	Age years	Age of onset in years	Seizure duration months	Onset of EPC from first seizure months	Other seizure types	Focal deficit	MRI Changes	Number of ASM	Rituximab after disease onset in months	Present status	Follow-up MRI
1	9.7	8	16	6	Focal impaired awareness	Yes	Paramedian frontal hyperintensity	3	17	Underwent Hemispherotomy; seizure-free; Mild hemiparesis	
2	8	8	1	3 weeks	-	Yes	Paramedian frontal hyperintensity	3	1	Seizure-free; no deficits	No progression
3	12	11	12	2	-	No	Frontal atrophy with paramedian Frontal hyperintensity	3	12	No focal deficits, only rare focal seizures without impairment of awareness	Mild progression
4	14	11	36	4	-	Yes	Right insular hyperintensity	5	12	Intermittent face EPC, no worsening of deficits	
5	32	24	96	96	Focal impaired awareness	No	Right insular hyperintensity	4	96	Intermittent tongue and face EPC	Mild progression
6	25	24	12	11	-	No	Bihemispheric atrophy	4	12	No focal deficits, only rare focal seizures without impairment of awareness; No EPC	No progression
7	10	7	36	6	Focal impaired awareness	Yes	Right Cerebral atrophy	3	12	No seizures; Deficits static; No EPC	
8	21	9	108	No	Focal impaired awareness	No	Left cerebral atrophy predominantly left fronto-opercular region	3	108	Rare Seizures; No EPC; No focal deficits	No progression
9	10	8	24	No	Focal impaired awareness	No	Left cerebral hemiatrophy predominantly left fronto-opercular region	3	24	Seizure-free; No EPC	

EPC- Epilepsia partialis continua; ASM-antiseizure medication.

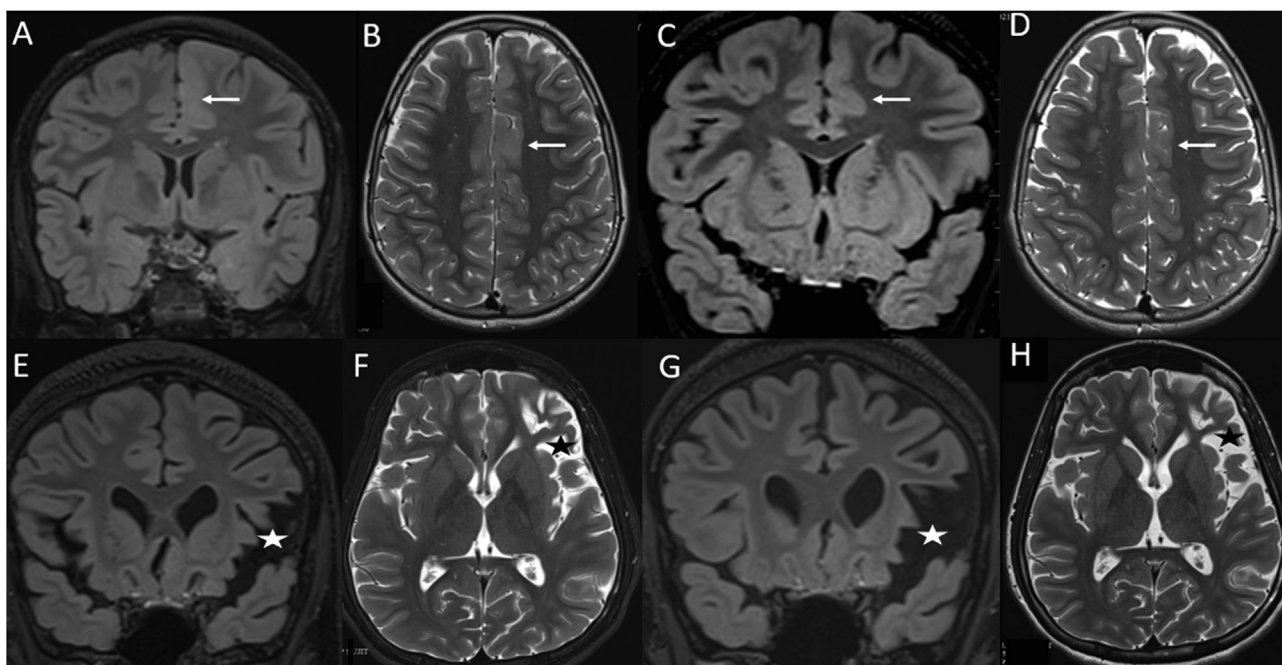


Fig. 1. FLAIR Coronal & B) Axial T2W image showing left medial frontal and cingulate cortex hyperintensity with blurring of gray-white matter junction C) FLAIR Coronal & D) Axial T2W image showing resolution of left medial frontal and cingulate cortex hyperintensity at 15 month follow up (case 2). FLAIR Coronal & F) Axial T2 W image showing left frontal and perisylvian cortex atrophy G) FLAIR Coronal & H) Axial T2 W image showing mild progression of left frontal and perisylvian cortex atrophy at 36 month follow up (case 3).

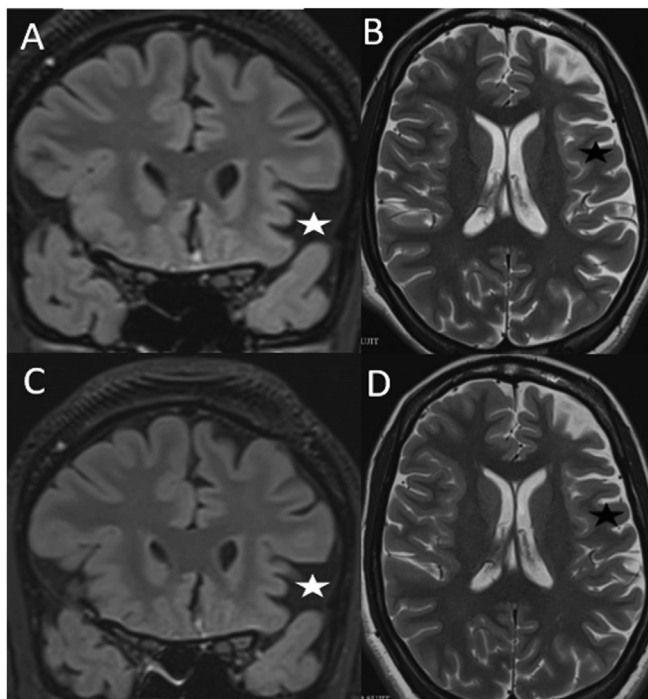


Fig. 2. A) FLAIR Coronal & B) Axial T2 W image showing left frontal and perisylvian cortex atrophy (star) C) FLAIR Coronal & D) Axial T2 W image showing no progression of left frontal and perisylvian cortex atrophy (star) at 13 month follow up (case 8).

Outcome

In one patient, motor deficits improved completely while in another patient, the deficit remained static. All patients without any deficits at time of onset, did not develop further deficits. EPCs resolved in four patients, but continued in two patients. The patients that continued to show EPC received rituximab late into the course of their illness (mean 66 months), while those showing resolution of EPCs received it early in the course of the disease (15.2 months). Eight patients remain on rituximab treatment, duration of treatment being 12 months to 24 months, (mean 14 months). None of the patients who received rituximab or oral or IV steroids developed status epilepticus. A post-rituximab MRI was performed after 12 months in five patients, which showed minimal or no progression of hemispheric atrophy compared to previous MRIs (Figs. 1 and 2). When we compared rituximab early in the course (within 12 months of onset of EPC, 5 patients) versus late (4 patients), two patients in the early group were found to be seizure-free compared to one in the late group. EPC stopped in three patients in the early group and 1 in the late group. In the early group, two did not develop focal motor deficits, two patients did not develop progression of their prior focal motor deficits and deficits improved in one. MRI showed mild progression in one and no progression in three in the early group.

Discussion

Antiseizure medications, immunotherapy and surgery are three mainstays of treatment for patients with RE [5,8]. Early Immunomodulatory therapy can result in seizure freedom, preservation of neurological function and delays surgery, but may potentially be associated with loss of the functions represented by the affected hemisphere [8]. Therefore, the question of medical management is important. The etiology is unknown in RE but pre-

sumed to have a neuro-inflammatory pathological basis. Rituximab has been widely used in rheumatoid arthritis and vasculitis as well as autoimmune encephalitis, anti-MUSK myasthenia gravis, relapsing remitting multiple sclerosis, neuromyelitis optica spectrum disorder and other neuroinflammatory disorders [20]. Its rapid onset of action, good safety profile and established efficacy in other neuroinflammatory disorders, makes it a good choice for treatment of RE. We describe a series of nine patients, two of whom had adult-onset RE with a beneficial effect on seizure burden with seizure freedom in 3/9. It was especially useful in 4/9 patients with EPC, 4/9 with no motor deficits, no worsening of deficits in 2/9, and halting evidence of neuroimaging progression in 5/9. No patient developed status epilepticus after receiving rituximab therapy.

In the study by Thilo et al. [11], patients with RE, having frequent episodes of focal motor status epilepticus improved with rituximab achieving seizure freedom for 6 months and a 6 months period involving non-disabling seizures. In the study by Lockman et al. [12], a 25-year-old female with a 4 year history of epilepsy and EPC, showed improvement with rituximab which lasted approximately 1.5 years after the first treatment and four months after the second noting less sustained improvement after the second treatment. (Table 2) In the case series of three patients with adult-onset RE by Castellano et al. [13], two received rituximab, one showed some response to rituximab, and one did not show any improvement. In a study by Liba et al. [10], one patient received rituximab after 9 months with an unsatisfactory response and underwent surgery. In our study, rituximab helped in the resolution of EPC in two patients and control of EPC in four patients. MRI also showed either none or had limited progression in five patients. Rituximab was well tolerated in our study group without any adverse events. The mean duration of initiation of treatment was 12 months except for 2 patients. This compares to other studies, where it was started late into disease or after patients developed drug resistant epilepsy. Only one of our patients required surgery after receiving rituximab. In this case, rituximab was initiated after the patient developed drug resistant epilepsy.

In previous studies of patients who received rituximab, this was late in the disease process and usually after trial of other immunotherapies. All patients showed improvement in control of seizures, arrest or slower progression of cognitive and motor decline, except for three patients [13,17,19]. (Table 2) In our study, complete recovery of deficits in one patient who received rituximab within one month of illness, suggests early therapy may reverse motor deficits. Patients in the study by Lockman et al., El Tawil et al. and Vijyanan et al. also showed improvement in motor weakness. In the study by Vijyanan et al. [16], patients remained seizure-free for 6 years as well noting that motor deficits stabilized after rituximab. Laxer et al. [18], showed a favorable response in eight of nine patients who received weekly IV infusions of rituximab (375 mg/m²) for 4 weeks in one or two courses (separated by six months). The response was present in the form of seizure reduction (50–100%) and reduced seizure severity as well as cognitive and/or motor functioning. Feyissa et al. [21], reported a 32-year adult onset RE patient, whose seizures were well controlled for 4 years with Rituximab, but subsequently had worsening and was treated with brain responsive neurostimulation. Herring et al. [18], reported five cases treated with rituximab, with improvement in seizure burden for the initial 1–2 years in all individuals. One patient had complete resolution of EPC and one had complete resolution of seizures after 2 years. The dose and duration of rituximab therapy was not standardized, and most studies had given only two doses at initiation and few who used rituximab for long term therapy. In our study, we have used repeated rituximab infusion over a minimum of one year duration which also might have helped in controlling disease activity and prevention

Table 2
Summary of previously published cases of Rasmussen's encephalitis treated with Rituximab.

Study	Age of onset in years	Number of patients	EPC onset after onset of seizure in years	Rituximab after disease onset in years	Response to Rituximab	Rituximab Dose
Thilo, B. et al. [11]	13	1	20	7	Seizure-free for 6 months and a further 6 months of non-disabling seizures	375 mg/m ² weekly for 4 weeks, then after 6 months
Lockman et al. [12]	21	1	25	6	1st course: seizure-free for 17 months, improved right hand function After 2nd course: partial response- no seizures for 4 months then recurrence	375 mg/m ² weekly for 4 weeks requiring intermittent plasma exchange
Castellano et al. [13]	Case 1 53 Case 2 44	3	57 12	4 3	No response Seizure frequency reduced to once weekly Did not receive	1000 mg
El Tawil et al. [14]	Case 3 47 43	1	61	18	Reduced seizure frequency and intensity; sustained improvement in arm function and speech output	375 mg/ m ² weekly for 4 weeks
Timarova et al. [15]	17 years	1	4	4	Reduced seizures to 2–3 focal brief seizures but no GTCs for 18 months After 2nd course focal seizure- 1/day and no GTCs	3 weekly course 375 mg/m ² After 6 months: increased seizure to 6/day so 2nd course given
Vijaya et al. [16]	42 years	1	13	13	Seizure-free for 6 years, improved weakness and speak few words	500 mg/dose × 4 doses 4 weeks apart, as well as on mycophenolate mofetil
Sansevere et al. [17]	6	1	5	5	No response	Right hemispherectomy after 3 months of Rituximab
Laxer KD et al. [18]	9 Cases Age – 6–22	9			8 had good response One underwent a functional hemispherectomy 3 months following treatment, continued to have seizures	weekly for four doses (375 mg/m ² ; 5 had one treatment and 4 received two treatments, 6 months apart
Liba et al. [19]	7	1	8	2	No response cognitive and motor deterioration, underwent hemispherotomy 4 year into illness	
Feyissa et al. [21]	32	1		7	For 4 years good response, then worsening	Responsive neurostimulation
Doniselli et al. [22]	20	1			No response	Limited cortical resection with good response
Herring et al. [23]		5			All had improvement in seizure burden for 1–2 year initially, one patient had complete resolution of EPC, one had complete resolution of seizures after 2 years	
Peariso et al. [24]	12	1	6–8 months	6–8 months	No response, bilateral disease	Four-week course

EPC- Epilepsia partialis continua, GTCs- Generalized tonic convulsion.

of relapse. None of our patients were on other immunosuppressive agent (e.g., oral or monthly steroids) which is an important advantage of rituximab. Two of our patients did not develop EPC on rituximab, suggesting it can prevent or delay onset of EPC. So, early initiation in patients with RE without EPC, might prevent onset of EPC as well as development of motor deficits. Follow up MRI in five patients also showed either stable disease or mild progression, suggesting potential effectiveness with rituximab to arrest the disease progression. All these findings warrant a further reporting though a prospective randomised controlled trial with a larger number of patients receiving rituximab as a treatment for RE early in the disease process may be logistically challenging.

The main limitation of the study is the retrospective study design, with clinical and imaging data collected only for clinical management. The treatment with rituximab was determined by the patients' clinical condition and ineligibility for surgery. The age of onset was not uniform and we included both childhood and adult-onset patients with RE. A major strength of our study is the beneficial effect especially on EPC when early initiation of therapy is begun. Because the number of patients was small, statistical significance was unable to be determined.

Conclusion

To our knowledge, this is the largest series of RE to date about the use of rituximab in RE. We suggest the use of rituximab be started within the initial year of disease onset, and as a result may lead to better control of seizures and greater stability of disease progression. Prospective comparative assessment between rituximab treated and untreated patients with RE may further support our results.

Ethical statement

This observational study was approved by an institutional ethical standards committee on human experimentation. A written informed consent was obtained from all participants (or guardians of participants) in the study for research purpose.

Conflict of interest.

Nil.

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