CASE STUDY

Rasmussen's Syndrome in a 9-Year-Old Filipino Treated with IVIG and Rituximab

Krystle V. Rustia, Ma. Marisse D. Dizon, Mel Michel G. Villaluz

Rasmussen's syndrome is a neuroimmune disease characterized by progressive unilateral cerebral dysfunction, for which hemispherectomy remains the definitive treatment. We report a 9-year-old right-handed Filipino girl with drug-resistant focal seizures, epilepsia partialis continua, and progressive right hemiparesis due to left hemispheric involvement. Epilepsy surgery was not immediately feasible because of parental concerns and logistical constraints in this resource-limited setting. Despite treatment with multiple antiseizure medications, seizures remained uncontrolled, prompting initiation of immunotherapy with intravenous immunoglobulin followed by rituximab. Rituximab was associated with marked seizure reduction and functional improvement, highlighting its potential role in the management of Rasmussen's syndrome when surgery is not feasible.

KEYWORDS: *Rasmussen's syndrome, epilepsia partialis continua, IVIG, rituximab*

Correspondence: Clinical Trial and Research Division
Clinical Research Department
Philippine Children' s Medical Center Quezon Ave., Quezon City Philippines
Phone: (02) 8588 9900 local 1308
Email: ctrd@pcmc.gov.ph

The authors affirm that this manuscript is original, has been read and approved by all contributing authors, that each author meets the established criteria for authorship, and that the content represents a truthful and accurate account of the work conducted.

Disclosure: The authors declare that they have no financial interests or other potential conflicts of interest that could influence the content of this work. This study was presented at the PCMC Annual Research Forum in November 2024.

Introduction

Rasmussen's syndrome (RS) is a rare, chronic, immune-mediated and inflammatory neurological disorder, characterized by intractable focal seizures with progressive neurological deterioration and hemispheric atrophy on imaging (1). It has an estimated incidence of 2.4 cases per 10 million individuals aged 18 years old or younger per year (2). Although RS has been extensively studied in other parts of the world, this disease entity is uncommon in the Philippines and little knowledge is known regarding its diagnosis and management. We present a case of a 9-year-old Filipino female with RS who underwent immunotherapy using IV Immunoglobulin (IVIg) and rituximab.

Case Summary

A previously developmentally at par 9-year-old, right-handed Filipino female presented with recurrent and persistent focal motor clonic seizures.

History began in 2017, at five years old, when she had her first focal status epilepticus characterized as clonic movement of the right arm with impaired awareness. This was accompanied by undocumented fever and vomiting. She was admitted and phenobarbital was initiated, resulting in seizure resolution. Cranial CT scan and CSF analysis were unremarkable, while video EEG revealed intermittent focal slowing in the left temporal region and generalized background slowing. She was discharged without seizure recurrences or neurologic deficits.

In 2018, at six years old, her mother noted she walked with a rightward lean, but can still write and converse. Recurrence of the same focal motor seizures prompted admission. Upon examination, right hemiparesis was noted. Cranial MRI with contrast showed T2/FLAIR hyperintense signals without restricted diffusion or contrast enhancement on the parasagittal portions of the left frontal lobe, suggestive of cerebral swelling. There is also mild degree of cerebral hemiatrophy on the left (Figure 1). EEG showed continuous slowing of the left hemisphere with focal epileptiform discharges seen over the left frontocentral, centroparietal and temporal areas Due to persistent seizures despite phenobarbital, levetiracetam, topiramate, and clonazepam were added, with referral to epilepsy service for suspected Rasmussen's Syndrome.

In 2019, her seizures worsened, and her right hemiparesis progressed with noted left hand preference. Language skills remained intact. Valproic acid was added resulting in good seizure control. Repeat Cranial MRI showed progression of the left hemispheric

atrophy (Figure 2), and repeat EEG captured focal motor seizures with onset coming from the left frontotemporal and frontocentral regions (Figure 3). Based on clinical, neuroimaging and EEG findings, Rasmussen's Syndrome was diagnosed. A 5-day course of IV methylprednisolone led to seizure reduction.

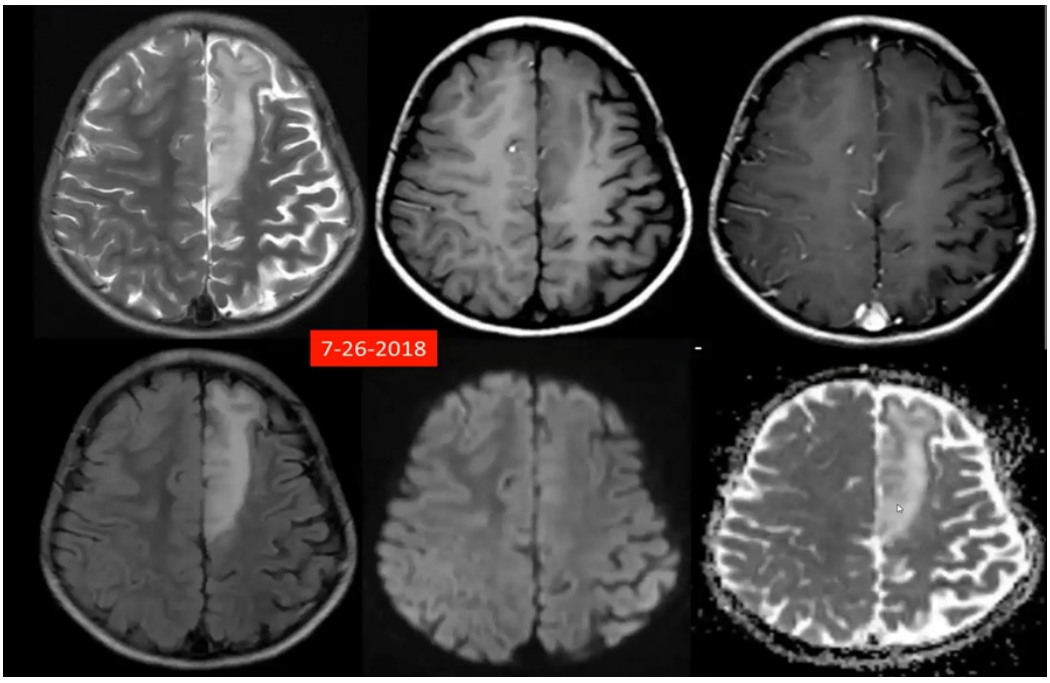

Figure 1. *Cranial MRI done in 2018 showing T1 hypointense, T2/FLAIR hyperintense region on the left parasagittal area of the frontal lobe (arrow), with no restricted diffusion or contrast enhancement. Mild left cerebral hemiatrophy is likewise seen.*

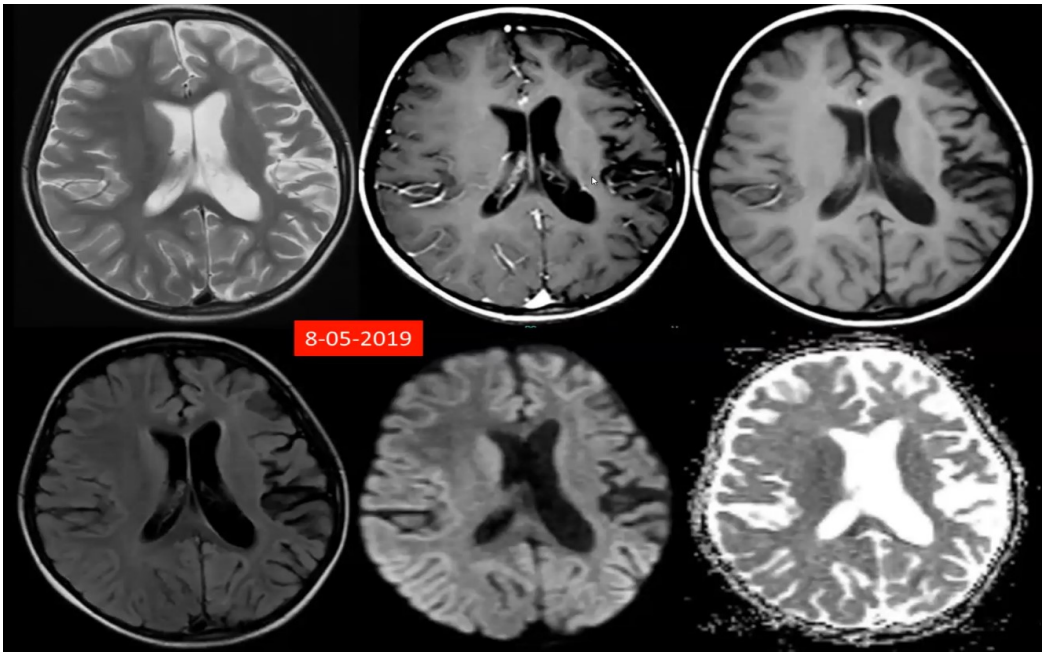

Figure 2. *Cranial MRI in 2019 showing progressive left cerebral hemiatrophy, without evidence of contrast enhancement.*

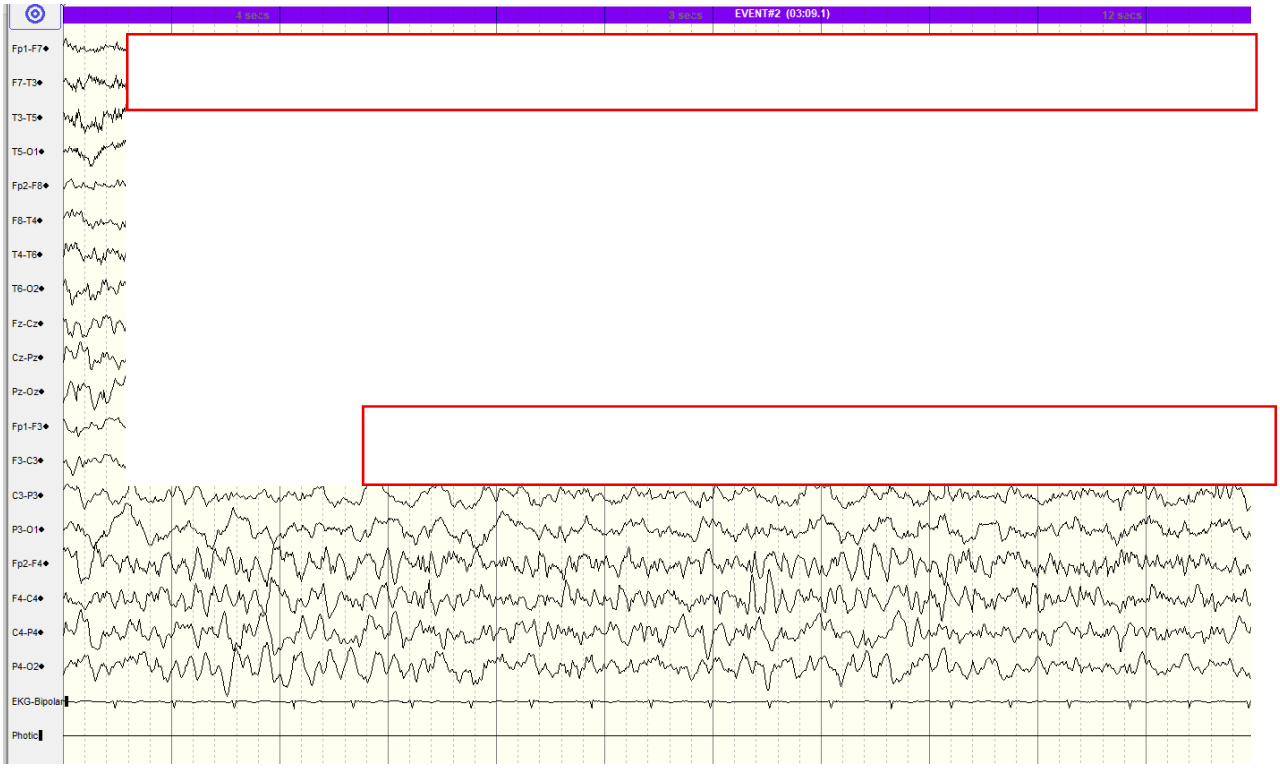

Figure 3. *EEG documenting a clinical event seen as focal motor clonic seizures of the right arm. The clinical event correlated with EEG findings showing run of ictal rhythm over the left frontotemporal regions eventually spreading to the left frontocentral regions.*

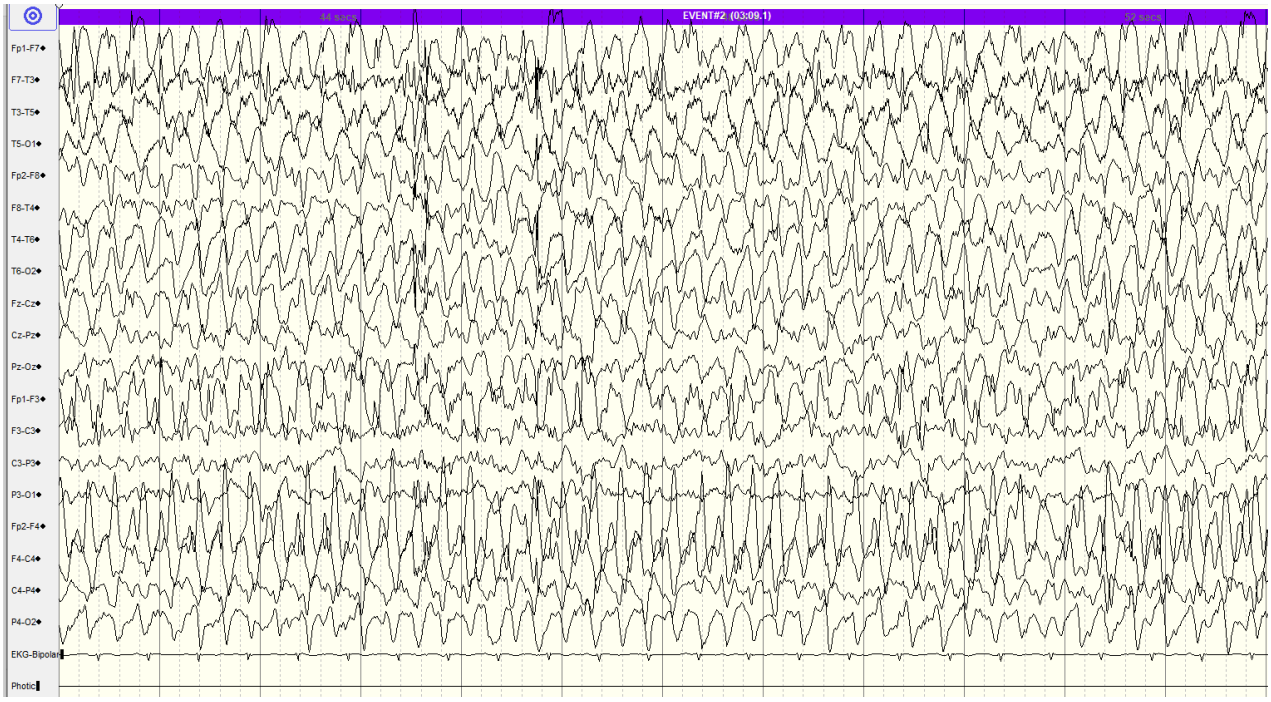

Figure 3. *(continuation) Discharges becoming generalized*

Over the next three years, her seizures and neurological deficits were initially well-controlled. However, in 2022, she was readmitted due to poorly controlled seizures, epilepsia partialis continua (EPC), and worsening neurological function. She developed Broca's aphasia and became wheelchair-bound due to progressive right hemiparesis. A repeat cranial MRI with contrast showed interval progression of the hemiatrophy of the left cerebral hemisphere (Figure 4). Repeat EEG showed slower background at 0.5-3 Hz over the left hemisphere and 4-6 Hz on the right. (Figure 5). Multiple clinical events were likewise seen with onset coming from the left frontocentral region, correlating with the patient's focal clonic seizures of the right hand (Figure 5). Intravenous immunoglobulin (IVIg) was given at 2g/kg divided in five days. There was partial improvement of her symptoms, hence Rituximab infusion at a dose of 375mg/m2 BSA weekly for four doses was initiated which significantly decreased seizure frequency by 80-90%. A repeat 2-hour EEG post-Rituximab was done which showed improved background activity, without any electrographic seizures, epileptiform discharges or clinical events noted (Figure 6).

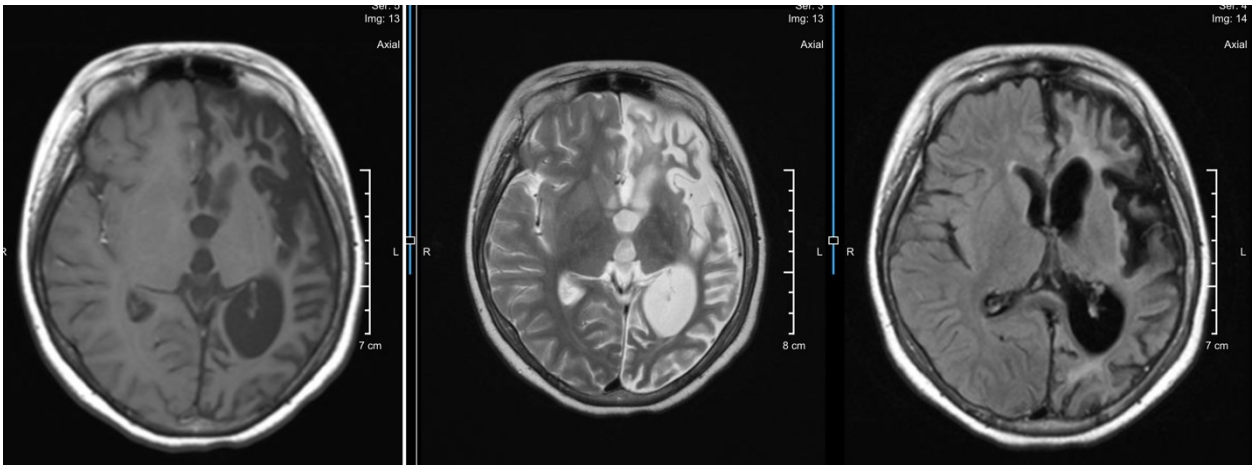

Figure 4. *Cranial MRI done on 2022. (A) T1W (2) T2W (3) T2W/FLAIR showing progression of the volume loss over the left frontotemporoparietal region*

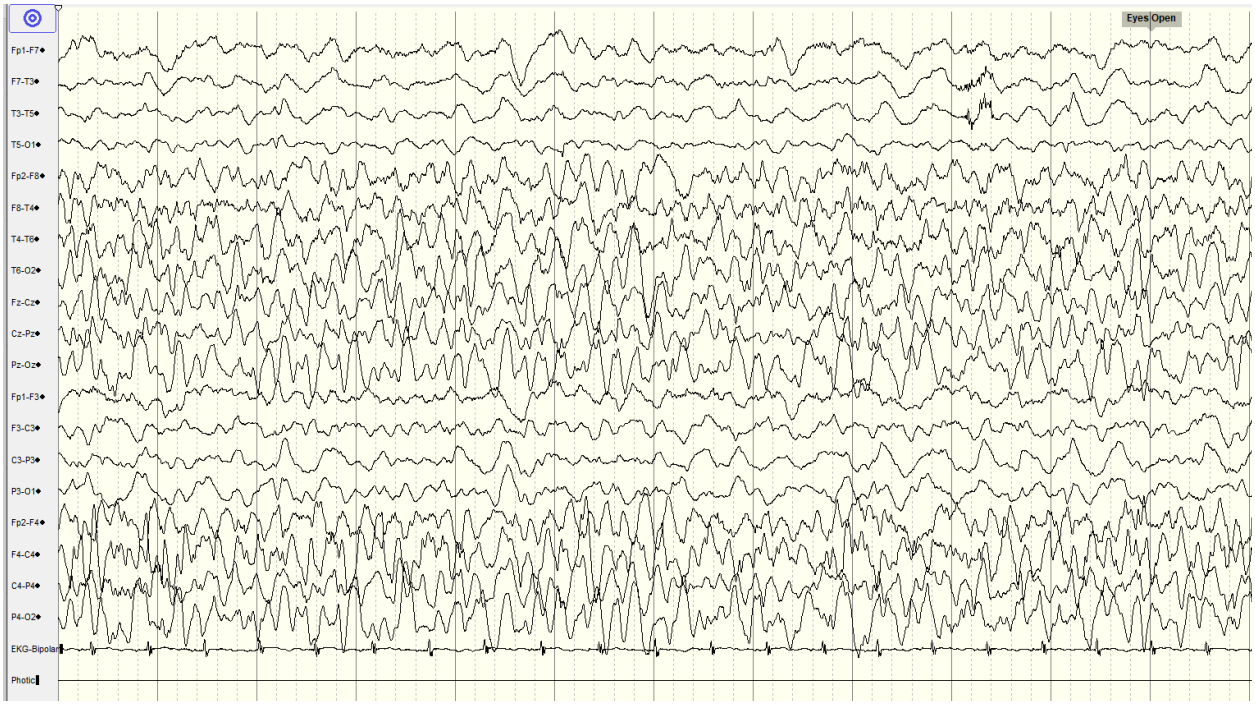

Figure 5. *EEG done pre-immunotherapy in 2022 showing background asymmetry showing continuous delta slowing over the entire left hemisphere and theta with higher voltages noted over the entire right hemisphere.*

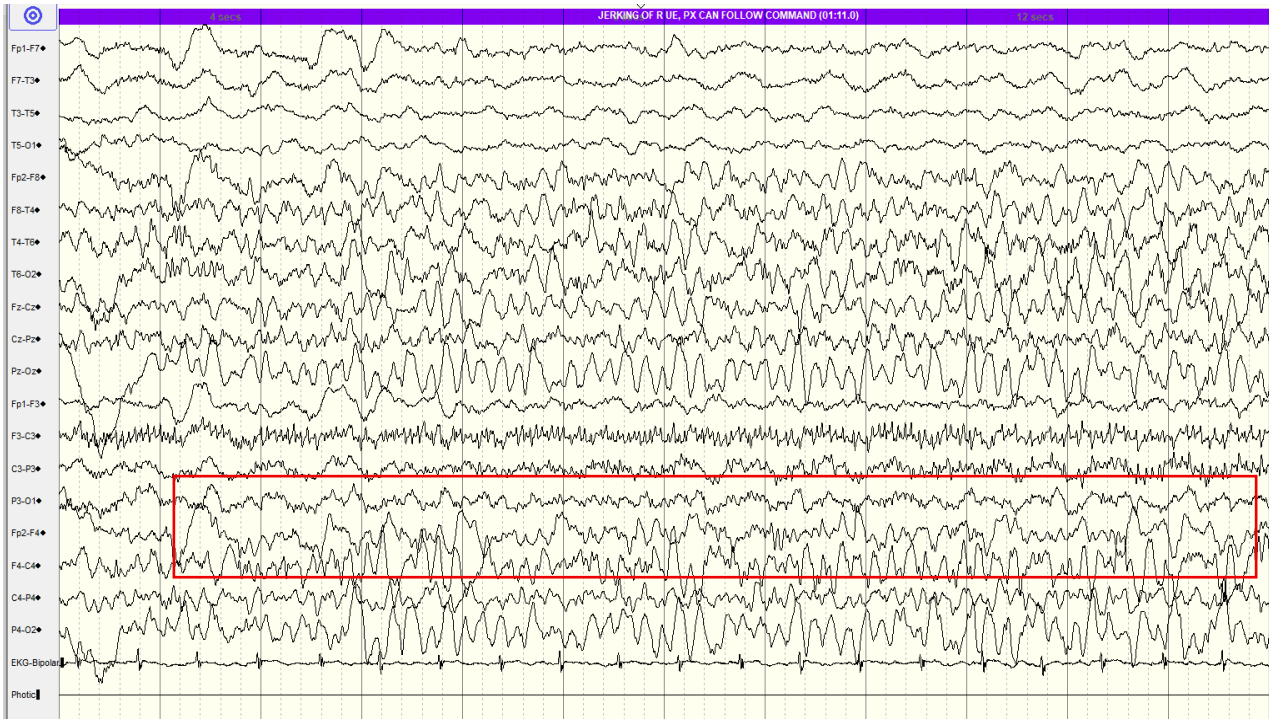

Figure 5. *(continuation) Clinical event noted as focal clonic movement of the right hand with electrographic correlate showing runs of 15-20 Hz fast activity coming from the left frontocentral and left centroparietal regions*

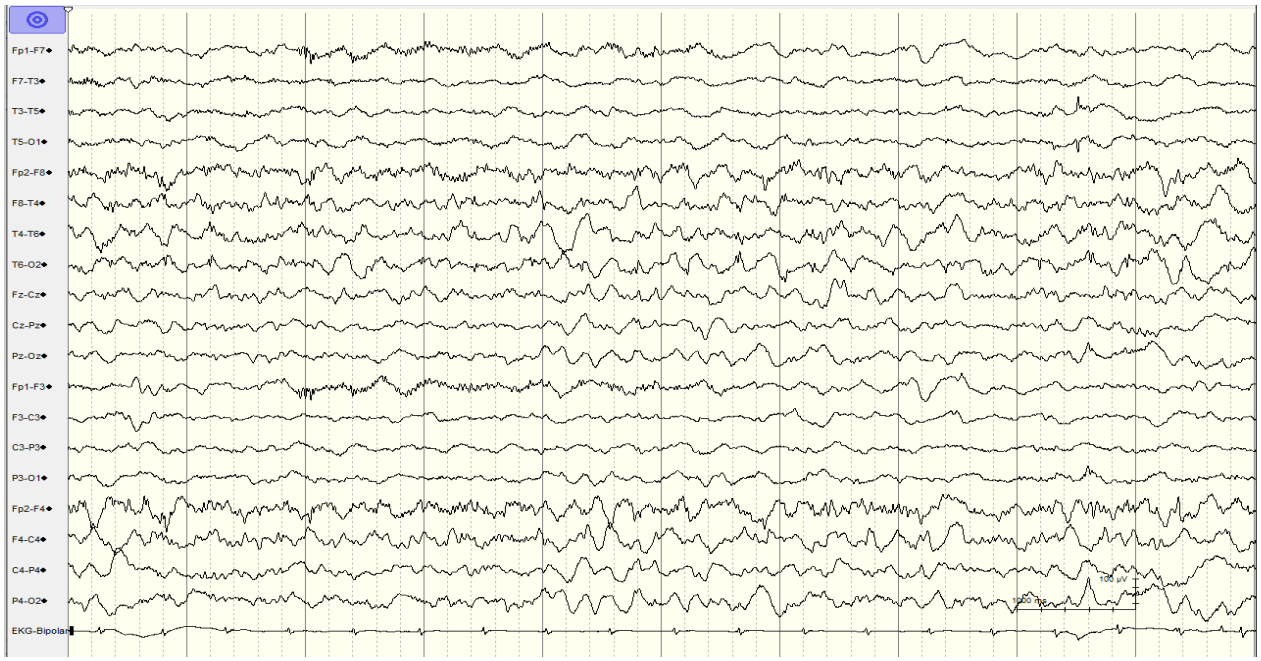

Figure 6. *Prolonged EEG done post-immunotherapy (IVIg and Rituximab). There was continuous delta slowing of the entire left hemisphere and there was higher voltages theta activity of the right hemisphere admixed with occasional 8-9 Hz alpha activity. No epileptiform discharges or electroclinical event noted in this recording.*

She was discharged with plans of rituximab infusion every six months, however delays in infusion were encountered due to bouts of respiratory infections. Eventually, she had two more doses of rituximab in 2023 and 2024, and is maintained on maximal tolerable doses of levetiracetam, valproic acid and perampanel which provided good seizure control. Her latest EEG in 2024 showed improved background activity on the right hemisphere (6-8Hz) and 2-4 Hz in the left hemisphere. Her seizure breakthroughs are now rare, occurring once or twice a year, mostly focal aware and triggered by infections. Her motor strength improved, and she ambulates independently with mild rightward leaning. Language is functional, though limited to short phrases with word-finding difficulty.

Discussion

Rasmussen's syndrome (RS) is a rare chronic neurological inflammatory condition characterized by drug-resistant focal seizures, progressive hemispheric dysfunction and MRI finding of cerebral hemiatrophy. Its symptoms begin during early childhood. The pathophysiology is primarily driven by cytotoxic $CD8^+$ T-cell infiltration and microglial activation, with autoantibodies such as anti-GluR3 playing a secondary role (3). Histopathological study of the affected cerebral hemisphere also showed multiple lymphocytic infiltrates

which are primarily CD3, CD8 T cells that causes neuronal destruction, tissue necrosis and eventually neuronal death and apoptosis (4).

According to the International League Against Epilepsy (ILAE), the diagnosis of Rasmussen's encephalitis requires a combination of clinical, EEG, and imaging findings (5). Bien et al. (3) proposed the core criteria in the diagnosis of RS which include focal seizures (with or without epilepsia partialis continua) and unilateral cortical deficits such as hemiparesis or aphasia. Supportive features include unilateral slowing or epileptiform activity on EEG and characteristic MRI findings—progressive unihemispheric cortical atrophy and T2/ FLAIR hyperintensities or atrophy of the ipsilateral caudate head. MRI is considered essential for diagnosis, as it confirms structural and inflammatory changes and helps distinguish Rasmussen's from mimics (3).

Treatment options to delay neurological deterioration in RS include medical and surgical management. Surgical hemispherectomy or hemispheric disconnection is the only intervention proven to halt RS progression and render patients seizure-free. In a 2023 study by Nava et al. (6), almost 60-70% of patients who underwent functional hemispherotomy achieved seizure freedom, with significant postoperative motor recovery. Meanwhile, language and cognitive outcomes are influenced by patient age and the hemisphere involved, with poorer outcomes observed when the dominant hemisphere is affected. In our case, the left (dominant) hemisphere was involved in a right-handed child, raising concerns about potential language deficits post-surgery. Additionally, the lack of institutional facility and expertise to perform epilepsy surgery at the time of diagnosis limited us in offering this procedure.

Immunotherapy—most often corticosteroids—were employed to delay progression, especially when surgery is not feasible or is deferred. Initial treatment with corticosteroids showed short-term improvements in seizure control, motor function, and slowing of cerebral atrophy (7). However, long-term follow-up show that these benefits may not be sustained, as many patients later experience relapses requiring surgical intervention (8).

Other immunomodulatory agents used were intravenous immunoglobulin (IVIg), tacrolimus and rituximab (7). Intravenous immunoglobulin has been widely used for immunodeficiency states as it contains variables variable amounts of proteins and contain natural antibodies that target T- and B -lymphocytes (9). Studies on the use of IVIg

for RS showed seizure-free rate of about 23% (10), however has tendency as well to lose its received IVIg with minimal improvement, prompting consideration of alternative immunotherapy.

Rituximab, an anti-CD20 monoclonal antibody (11), was administered to our patient following limited response to IVIG. Since its first reported use in RS in 2008 (12), subsequent case series have demonstrated its potential benefits. In a 2022 single-center review by Jagtap et al. (13), most RS patients showed marked seizure reduction and resolution of EPC after rituximab treatment. Better outcomes were observed when rituximab was initiated early (mean ~32 months from disease onset), with MRI progression stabilizing or reversing in nearly 60% of patients. In reports, many centers use rituximab as second-line or adjunctive therapy, often in a 375 mg/m² weekly for four weeks as induction regimen followed by maintenance dosing (e.g. every six to twelve months) (13,14). Case reviews also show that rituximab is well tolerated and has no reported serious adverse effects. Long-term outcome data are still limited but reported case series suggest sustained benefit with ongoing treatment of Rituximab. Rituximab may improve seizure burden and disease progression in RS, although larger studies with longer follow-up are needed to further characterize its utility.

Conclusion

We report our institution's first Filipino case of a 9-year-old right-handed girl diagnosed with Rasmussen's Syndrome and had progressive neurological decline and worsening seizures, ultimately treated with rituximab. Treatment resulted in marked seizure reduction, resolution of EPC, and improvement in language and mobility. This case highlights the potential role of rituximab as an effective and accessible immunotherapeutic option, particularly in resource-limited settings.

References

1. Varadkar S, Bien C, Kruse C, Jensen F, Bauer J, Pardo C, et al. Rasmussen's encephalitis: clinical features, pathobiology and treatment advances. Lancet Neurology. 2014; 13(2): 195-205.

2. Bien C, Tiemeier H, Sassen R, Kuczaty S, Urbach H, von Lehe M, et al. Rasmussen encephalitis: incidence and course under randomized therapy with tacrolimus or intravenous immunoglobulins. Epilepsia. 2013; 54(3): 543-550.

3. Bien C, Granata T, Antozzi C, Cross J, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. Brain. 2005; 128(Pt 3): 454-71.

4. Bien C, Bauer J, Deckwerth T, Wiendl H, Deckert M, Wiestler O, et al. Destruction of neurons by cytotoxic T cells: a new pathogenic mechanism in Rasmussen's encephalitis. Annals of Neurology. 2002; 51(3): 311-8.

5. Riney K, al e. ILAE Website. [Online].; 2021 [cited 2024 December 9. Available from: https://www.ilae.org/files/dmfile/Riney_VariableAges_7Apr21.pdf.

6. Nava B, Costa U, Hamad A, Garcia C, Sakamoto A, Aragon D, et al. Long-term seizure outcome and mobility after surgical treatment for Rasmussen encephalitis in children: A single-center experience. Epileptic Disorders. 2023; 25(5): 749-757.

7. Lagarde S, Boucraut J, Bartolomei F. Medical treatment of Rasmussen's Encephalitis: A systematic review. Review Neurologique. 2022; 178(7): 675-691.

8. Bahi-Buisson N, Villanueva V, Bulteau C, Delalande O, Dulac O, Chiron C, et al. Long term response to steroid therapy in Rasmussen encephalitis. Seizure. 2007; 16(6): 485-92.

9. Dourmishev L, Guleva D, Miteva L. Intravenous immunoglobulins: Mode of action and indications in autoimmune and inflammatory dermatoses. Int J Inflam. 2016.

10. Takahashi Y, Yamazaki E, Mine J, Kubota Y, Imai K, Mogami Y, et al. Immunomodulatory therapy versus surgery for Rasmussen syndrome in early childhood. Brain Dev. 2013; 35(8): 778-85.

11. Weiner G. Rituximab: mechanism of action. Semin Hematol. 2010; 47(2): 115-23.

12. Strozzi S, Mathis J, Wiest R, Pollo C, Steinlin M. Rituximab in rasmussen encephalitis. Neuropediatrics. 2008; 39: 10.

13. Jagtap S, Patil S, Joshi A, Kurwale N, V J, Y D. Rituximab in Rasmussen's encephalitis: A single center experience and review of literature. Epilepsy & Behavior Reports. 2022; 19: 100540.

14. Thilo B, Stingele R, Knudsen K, Boor R, Bien C, Deuschl G, et al. A case of Rasmussen encephalitis treated with rituximab. Nat Rev Neurol. 2009; 5(8): 458-62.

15. Herring R, Messinger M, Coorg R. Effect of Rituximab on Seizure Burden in Patients with Rasmussen Encephalitis: A Case Series. Neurology. 2018; 90(15): 5.