

Case Report

Adult-onset Rasmussen's Syndrome with associated cortical dysplasia

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ABSTRACT

We describe a 23-year-old woman with previous right temporal lobe surgeries for underlying cortical dysplasia, presenting with **drug-resistant** right hemispheric seizures and epilepsy partialis continua (EPC). After anti-seizure medication adjustments, she developed focal status epilepticus with progressive EEG and neuroimaging changes. Cerebrospinal fluid and serum autoimmune panels were negative except for an elevated serum acetylcholine-receptor antibody titer, but she underwent immunosuppressive therapy. Stereotactic-EEG evaluation demonstrated multifocal independent ictal patterns in the right hemisphere. Rasmussen's Syndrome was confirmed by brain biopsy, and a hemispherectomy was performed. This patient demonstrates the rare association of adult-onset EPC with cortical dysplasia, precipitously evolving into Rasmussen's Syndrome.

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1. Introduction

Rasmussen's Syndrome (RS) commonly presents without underlying primary pathology or etiology [1–3]. Nonetheless, cortical dysplasia has been noted increasingly on MRI and pathological examination in patients with RS [3,4]. Although the association of RS with cortical dysplasia is often identified retrospectively, a recent report describes the fulminant presentation of chronic-progressive epilepsy partialis continua (EPC) in an adolescent with inflammatory changes in the adjacent dysplastic cortex [5]. We describe an adult woman who developed chronic focal epilepsy due to right temporal lobe cortical dysplasia. She underwent two unsuccessful temporal lobe resections, and, after the second, presented with new-onset epilepsy partialis continua (EPC) confined to her lower face. Following admission to the hospital for video-electroencephalography (EEG) monitoring and anti-seizure medication changes, she developed focal status epilepticus, demonstrating the fulminant transformation of her chronic EPC into RS.

2. Case report

The patient was 19 years old, a healthy right-handed woman, when she presented with focal seizures and was found to have a right temporal

cortical lesion on brain MRI. The lesion was removed, demonstrating cortical dysplasia on histopathology. Her seizures resumed after a few months, initially as rare focal seizures without alteration of awareness, later becoming more frequent and severe, with loss of awareness and evolution to bilateral convulsive seizures. Two years after her first surgery, she underwent Phase I and II evaluations at an academic epilepsy center, the latter including extra- and intraoperative recordings with a combination of grid, strip and depth electrodes. She underwent an extensive right temporal lobectomy, consisting of an 8 cm lateral resection with an inferior parietal topectomy (Fig. 1, upper panel). During that evaluation, concerns were raised about the diffuse nature of the interictal and sub-clinical ictal activity. Postoperatively, she manifested a left-sided, upper and lower quadrant, visual field deficit. Again, her focal seizures with and without impaired awareness continued, but focal to bilateral convulsive seizures remitted. She also noted evolution of intermittent focal twitching of her lower face, which became chronic without spreading somatotopically.

Four years after her first surgery, at age 23 years old, she was examined at UT Health San Antonio. She was noted to have a chronic, but arrhythmic twitching of her left lower face. Additionally, she was having several discrete focal seizures per week, both with and without loss of awareness. She was on a combination of levetiracetam, lacosamide, phenytoin, topiramate and clonazepam. She complained of excessive fatigue, which she attributed to her medication regimen. Other than left lower facial weakness related to her EPC, and persistent left visual field defect, her neurological examination was normal. She was admitted for video-EEG monitoring to electroclinically characterize her seizure types,

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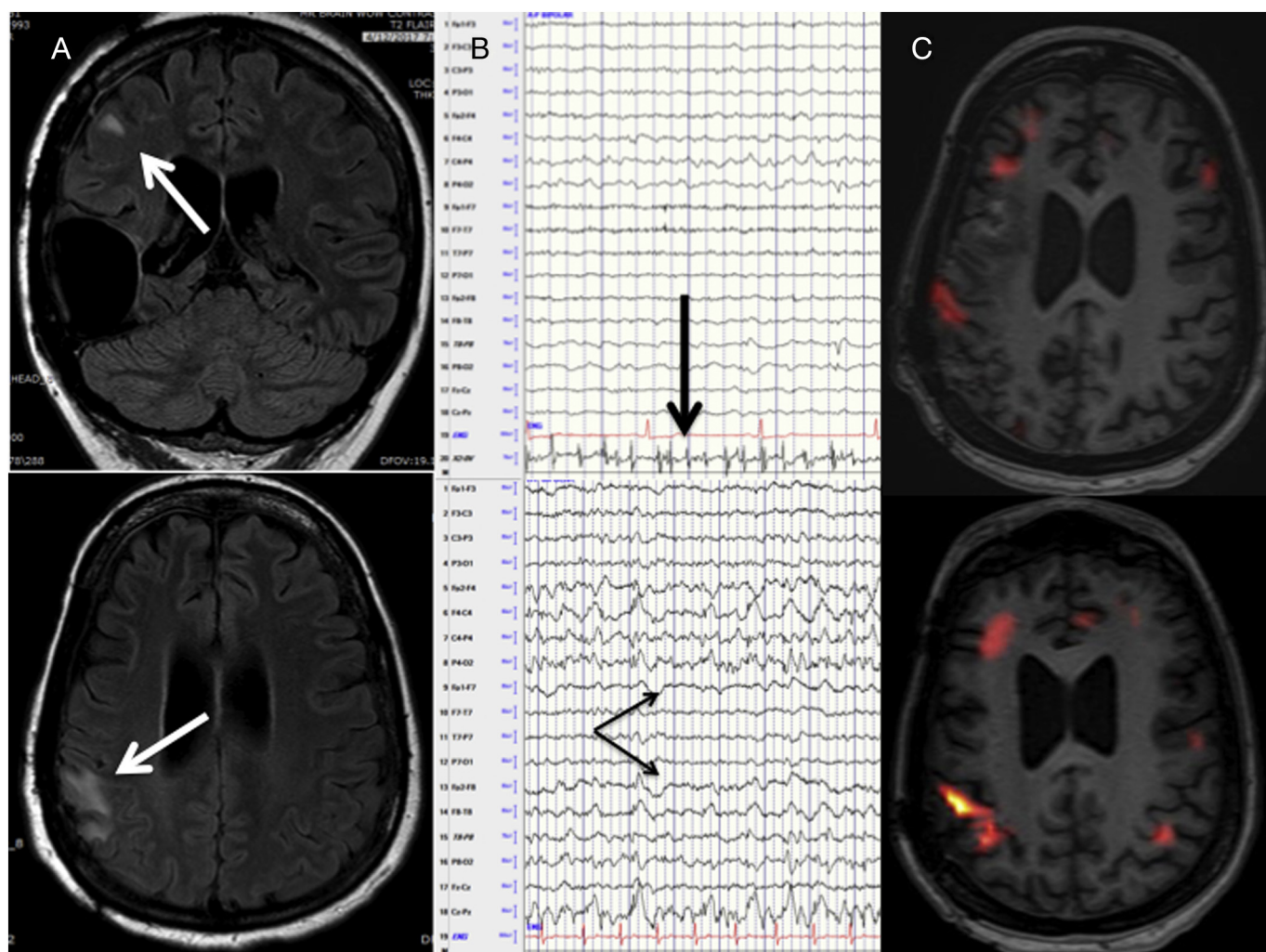


Fig. 1. Neuroimaging and EEG features of index case. Legend: Panel A depicts cortical signal increases (white arrows) at baseline, with a right temporal porencephalic cyst, Panel B shows EEG samples, including an “interictal sample” with clonic muscle artifact (thick black arrow), and example of ictal discharge lateralized to the right hemisphere, and Panel C demonstrates subtraction ictal SPECT scans indicating increased perfusion over the course of her focal status epilepticus (performed 4 weeks apart).

localize the seizure onset zone by EEG, obtain an ictal SPECT, and optimize her anti-seizure drug regimen.

Her interictal EEG demonstrated periodic epileptic discharges at 0.5–2 Hz frequency over the right posterior temporal and centroparietal regions (Fig. 1B, upper panel), which were rarely time-locked with the facial clonic artifact. We recorded typical seizures which began with a sensory aura consisting of her left arm or thigh tightening, followed by motor activity, ranging from left facial and hand clonic activity to focal tonic seizures, consistent with activation of the supplementary motor area, and left hemiclonic activity. The EEG onset was broadly noted over the right posterior hemisphere. An ictal SPECT was performed, which revealed right centroparietal and bilateral premotor activations (Fig. 1C, upper panel). As she developed a generalized rash acutely after introduction of a new anti-seizure medication in place of another, she changed back to her original regimen. However, her focal seizures gradually increased in frequency and severity, evolving into focal status epilepticus consisting of focal motor seizures involving her left face, arm and leg. After elective intubation, she was transferred to the intensive care unit to undergo trials with anesthetics, including ketamine, propofol and pentobarbital, with effective, long-term burst suppression being only achieved with the latter. She was also cycled through different anti-seizure drug combinations, including cannabidiol and the ketogenic diet in order to withdraw her from anesthetics. She demonstrated only an elevated acetylcholine receptor (muscle) antibody in the serum

(11.4 nmol/L, reference ≤ 0.02), but no other abnormalities on the serum or cerebrospinal fluid autoimmune panels (Mayo Clinic Laboratories, Rochester, MN). Immunological interventions were pursued starting the second week of anesthesia, including a five-day course of intravenous steroids, one week of intravenous immunoglobulin (IVIG) infusion and a complete course plasmapheresis after a thymectomy (enlargement identified incidentally). In the meantime, on scalp EEG, as well as repeat MRI and ictal SPECT scans of the brain, there was evidence of increased involvement of the insula and frontal lobes, including the contralateral hemisphere, but still no evidence of atrophy on MRI (Fig. 1, lower panels). While the progressive neuroimaging changes were consistent with RS, they could have also reflected remote effects of focal status epilepticus arising from the centroparietal operculum or insula. For that reason, we submitted her for continuous, intracranial 24-hour monitoring with stereotactically-implanted EEG electrodes sampling the right hemisphere, targeting the neuroimaging and scalp EEG abnormalities. Subclinical seizures and periodic discharges were recorded multifocally, which were in a large part asynchronous, most prominent over the residual temporal neocortex, as well as in the frontal, parietal and occipital cortices, but not in the insula nor cingulate. Laser thermocoagulation at precentral, parietal and temporal sites was attempted, but did not affect the ongoing repetitive discharges. Due to evidence of the diffuse cortical abnormalities on EEG and neuroimaging, the increasing risk of sepsis and progression of status-induced brain

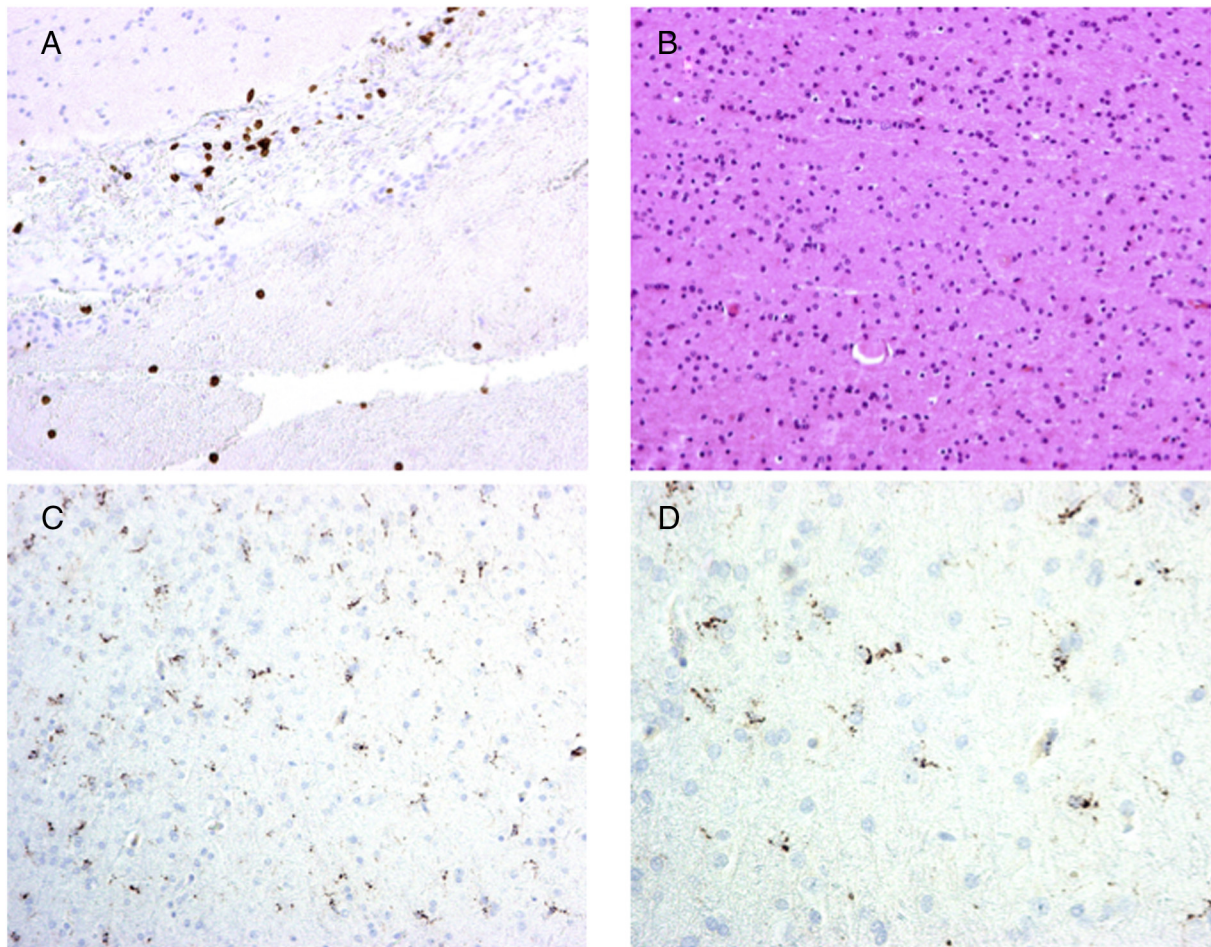


Fig. 2. Histopathological findings on frontal lobe biopsy. Legend: Panel A illustrates lymphocytes (CD68, 20 $\times$ and 40 $\times$, respectively); Panels B, C, and D illustrate microglia activation (HE) as do Panels C and D (CD68, 20 $\times$ and 49 $\times$, respectively).

injury, she underwent a right functional hemispherectomy. RS was confirmed histopathologically in frontal lobe specimens acquired by an open biopsy anterior to the laser ablation tracts (Fig. 2). As anticipated, the surgery resulted in left hemiplegia, transient left arm dysesthesias, and a complete left homonymous hemianopsia. She quickly recovered **strength and motility** movement in her right-sided extremities. She was seizure-free one year postoperatively on leviteracetam 1000 mg twice daily. She continues to recover strength and control of her left lower extremity and is able to ambulate with the help of an exoskeleton, but, as expected, her left hand remains plegic. The left hemispheric MRI signal abnormalities resolved by three months, but EEG still demonstrates right hemispheric interictal epileptiform discharges. The repeat acetylcholine receptor antibody titers were mildly increased after one year, and repetitive stimulation confirmed an electrodecremental response in the deltoids. Other than occasional ptosis, she has no definite symptoms of myasthenia gravis. It is possible that her previous complaint of excessive fatigue was an early symptom of myasthenia gravis, and that the thymectomy prevented her disease progression.

3. Discussion

This case underlines the heterogeneous presentation of Rasmussen's Syndrome (RS), both clinically and etiologically [1–3]. Our patient was initially diagnosed with right temporal lobe epilepsy due to cortical dysplasia, but over time, despite surgical interventions, the emergence of EPC marked a more diffuse involvement of the right hemisphere. Still,

as the EPC remained localized to her face over two years, her exam remaining neurologically intact, and the brain MRI without any evidence of right hemispheric cortical or subcortical atrophy, she did not fulfill the criteria for RS [2–4]. While about 50% of RS patients present with EPC [1], chronic progressive EPC is pathognomonic for RS [1–3,5]. Even her CSF examination did not indicate an inflammatory process. Our working diagnosis for the first weeks after her admission had been super-refractory focal status epilepticus, related to diffuse or multiregional cortical dysplasia not evident on her MRI.

The diagnosis of RS was suspected initially on the basis of progressive scalp EEG, SPECT and MRI changes over the entire right hemisphere during her hospitalization, although progressive functional and structural neuroimaging changes can be seen even in the setting of focal status epilepticus. While evidence of increased acetylcholine receptor antibodies in the serum, though not in the cerebrospinal fluid, did not support RS, it did reflect a propensity for auto-immunity. The most compelling finding, however, was provided by the stereotactic EEG examination, which demonstrated asynchronous and independent multiregional and -lobar periodic patterns reflecting a diffuse, multifocal potential for epileptogenesis, consistent with an inflammatory process. This multifocal process may have been apparent at the time of her second surgery, as described in the intracranial EEG reports, which was probably the main justification for the large temporal lobectomy and inferior parietal topectomy. So, in retrospect, it appears that our patient was already symptomatic of RS based upon the earlier intracranial EEG findings and the emergence of new-onset EPC in the setting of chronic drug-resistant epilepsy.

Functional hemispherectomy is becoming a more accepted treatment for **drug-resistant** hemispheric epilepsy in adults [6–8]. Almost all of the patients in recent case series were patients with unilateral atrophy or porencephaly, most commonly due to congenital or perinatal stroke. Few adult patients undergo hemispherectomy for RS, probably not only due to a milder course of adult-onset RS, but also because of its rare occurrence.

4. Conclusion

In summary, our patient demonstrated a late-onset, RS, which evolved from temporal lobe epilepsy due to underlying cortical dysplasia. The emergence of EPC in our patient should trigger a comprehensive screening for autoimmune encephalitides. However, as in this case, cerebrospinal studies are often negative [1,5]. Outpatient functional neuroimaging with SPECT or PET, in addition to brain MRI, can provide a baseline for measuring disease progression [9]. While earlier use of immunosuppressive therapies may have prevented disease progression and reduced the burden of anti-seizure medications [10], functional hemispherectomy provided an effective treatment for drug-resistant epilepsy in our patient.

Acknowledgments

This case study was presented at the American Epilepsy Society Meeting held in Washington, DC, in December 2017.

Disclosures

The authors have no conflicts of interest to disclose.

Ethical statement

Study Ethics and Patient Consent: This study was performed in accordance with “The Code of Ethics of the World Medical Association” and consent for publication of this case report was obtained from the patient.

References

- [1] Varadkar S, Bien CG, Kruse CA, Jensen CA, Bauer J, Pardo CA, et al. Rasmussen's syndrome: clinical features, pathobiology, and treatment advances. *Lancet Neurol* 2014; 13:195–205.
- [2] Bien CG, Granata T, Antozzi C, Cross H, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen syndrome: a European consensus statement. *Brain* 2005;128:454–71.
- [3] Olson HE, Lechpammer M, Prabhu SP, Ciarlini PDSC, Poduri A, Gooty VD, et al. Clinical application and evaluation of the Bien diagnostic criteria for Rasmussen syndrome. *Epilepsia* 2013;54:1753–60.
- [4] Takei H, Wilfong A, Malphrus A, Yoshov D, Hunter JV, Armstrong DL, et al. Dual pathology in Rasmussen's encephalitis: a study of seven cases and review of the literature. *Neuropathology* 2010;30:381–91.
- [5] Hohenbichler K, Lelotte J, Lhommel R, Tahry RE, Vrielynck P, Santos SF. Adult-onset Rasmussen syndrome associated with focal cortical dysplasia. *Epileptic Disord* 2017; 19:471–80.
- [6] Cukiert A, Cukiert CM, Argenton M, Baise-Zuang C, Forster CR, Mello VA, et al. Outcome of hemispherectomy in hemiplegic adult patients with refractory epilepsy associated with early middle cerebral artery infarcts. *Epilepsia* 2009;50:1381–4.
- [7] Schmeiser B, Zentner J, Steinhoff BJ, Schulze-Bonhage A, Kogias E, Wendling A-S, et al. Functional hemispherectomy is safe and effective in adult patients with epilepsy. *Epilepsy Behav* 2017;77:19–25.
- [8] McGinity M, Andrade N, Karkar K, Caron JL, Szabo C, Papanastassiou A. Functional hemispherectomy for status epilepticus in two adults. *World Neurosurg* 2016;93: 489.e11–6. <https://doi.org/10.1016/j.wneu.2016.06>.
- [9] Kuki I, Matsuda K, Kubota Y, Fukuyama T, Takahashi Y, Inoue Y, et al. Functional neuroimaging in Rasmussen syndrome. *Epilepsy Res* 2018;140:120–7.
- [10] Khurana DS. Focal epilepsies: immunologic and inflammatory mechanisms. *Semin Pediatr Neurol* 2014;21:207–13.