

Rasmussen's Encephalitis in a 58-Year-Old Female: Still a Variant?

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ABSTRACT: Background: We report the case of a 58-year-old female with clinical, radiological, and histopathological evidence of Rasmussen's encephalitis, representing the oldest confirmed case to date. **Case Summary:** The patient presented with complex partial seizures characterized by numbness of the left face and staring spells. These progressed to a state of *epilepsia partialis continua* with jerking of the left face, as well as severe cognitive impairment and loss of all communication. The patient responded well to Intravenous Immunoglobulin (IVIG) therapy despite early complications and with ongoing treatment is living independently with minimal cognitive impairment. **Conclusions:** This represents the oldest confirmed case of Rasmussen's encephalitis and suggests that this diagnosis should be considered in patients of any age with an appropriate clinical picture. We recommend IVIG as a first line therapy for adult cases of Rasmussen's encephalitis.

RÉSUMÉ: Encéphalite de Rasmussen chez une femme de 58 ans : une variante? Contexte : Nous rapportons le cas d'une femme de 58 ans présentant des signes cliniques, radiologiques et histopathologiques d'encéphalite de Rasmussen (ER), qui serait le cas confirmé le plus âgé rapporté jusqu'à maintenant. **Observation :** La patiente a consulté pour des crises d'épilepsie partielle complexe caractérisées par un engourdissement du côté gauche du visage et des absences épileptiques évoluant vers une épilepsie partielle continue avec secousses à l'hémiface gauche, déficit cognitif sévère et absence de toute communication. La patiente a bien répondu au traitement par gammaglobulines polyvalentes par voie intraveineuse malgré des complications précoces. Elle présente un déficit cognitif minime, vit de façon autonome et demeure sous traitement. **Conclusions :** Ce cas d'encéphalite de Rasmussen est le cas confirmé le plus âgé qui soit connu. Ce diagnostic devrait être envisagé chez les patients de tous âges ayant un tableau clinique suggestif de cette maladie. Nous recommandons les gammaglobulines polyvalentes par voie intraveineuse comme traitement de première ligne chez les adultes atteints d'ER.

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Rasmussen's encephalitis (RE) is generally considered to be a disease of childhood, with the vast majority of cases occurring in children less than ten years of age. However, there are at least 29 cases of adult or adolescent onset Rasmussen's in the literature¹⁻¹¹ (Table), with the oldest reported case to date occurring in a 54-year-old female.³ Despite a lack of strict diagnostic criteria, RE is generally accepted as the appropriate diagnosis in the setting of a chronic, progressive, focal encephalitis which is commonly accompanied by seizures (classically *epilepsia partialis continua* [EPC]), hemiparesis, and cognitive decline. Importantly, other causes of focal encephalitis such as active viral infection should be ruled out before a diagnosis of RE. There are several emerging reports of glutamate receptor autoantibodies as possible contributors to the pathogenesis of RE,¹¹⁻¹⁴ although antibodies are also found in other epilepsy subtypes and are not specific to RE.^{15,16} We report the diagnosis and management of a 58-year-old previously healthy female, with clinical, radiological, and histopathological

evidence of Rasmussen's encephalitis, representing the oldest confirmed case to date.

CASE REPORT

The patient was referred to our center following her first generalized tonic-clonic seizure. History revealed that she had suffered three episodes of complex partial seizures over the previous three months, each characterized by numbness of the left face and arm with decreased

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Table: Summary of adult cases of Rasmussen's encephalitis

Author (Year; ref)	Number of Patients (ages/sex)	Treatment	Outcome	Comments
Gray et al. (1987; 8)	1 (29/F)	Anticonvulsants	Died 2 years after onset of seizures	Biopsy and autopsy consistent with RE
McLachlan et al (1993; 2)	3 (36, 24, 16)	Cortical resection	Improved seizure control	All 3 biopsies positive for CMV
Hart et al (1997; 5)	13: 4 pts age 21-40 5 adolescents aged 13-16, 3 adults presenting as mass lesions	Anticonvulsants, surgery	Variable	
Leach et al (1999; 7)	2 (39/M, 33/F)	Steroids followed by IVIG	Striking improvements in cognition, seizure control, and motor function	Patient 2 not biopsy confirmed
Vadlamudi (2000; 3)	1 (54/F)	Anticonvulsants, steroids, IVIG, Gancyclovir	Ongoing seizures, cognitive decline, progression of MRI changes	Gadolinium enhancing lesions, not otherwise described. CSF normal
Hennessy et al (2000; 9)	2 (22/F, 31/F)	Temporal lobectomy	Stable with infrequent seizures, no further cognitive decline	Biopsies consistent with RE
Villani et al (2001; 4)	1 (45/F)	IVIG	Resolution of EPC, 75% reduction in seizure frequency, improvement of neurologic deficits	Onset of EPC 13 years after onset of disease
Wennberg et al (2003; 1)	1 (24/F)	Anticonvulsants	Stable for 5 years, clinically and on serial MRI	Biopsy consistent with RE
Granata et al (2003; 6)	1 (45/F)	IVIG	Resolution of EPC, 75% reduction in seizure frequency, improvement of neurologic deficits	Only adult patient in series of 15: Children showed less improvement with IVIG
Lagrange et al (2003; 10)	1 (40/M)	Anticonvulsants, 2 temporal lobe resections	Mild improvement but ongoing daily seizures	Presented with narcolepsy
Takahashi et al (2005; 11)	3 (23/F, 25/F, 28/F)	N/A	N/A	2 patients positive for antibodies to GluR ₂

EPC = Epilepsia Partialis Continua; F = Female; GluR₂ = NMDA Glutamate receptor ϵ 2 subunit; IVIG = Intravenous Immunoglobulin; M = Male; RE = Rasmussen's encephalitis

responsiveness and staring for 15-30 seconds. Physical examination was normal. Electroencephalogram (EEG) revealed periodic lateralized epileptiform discharges over the right region. Cerebrospinal fluid (CSF) analysis revealed 8 WBC/mm³ and was negative for herpes simplex virus DNA by PCR. Serologic testing was negative for acute CMV, VZV, HSV, and EBV infection. An MRI showed T2 hyperintensity in the right

temporoparietal region but no diffusion restriction on diffusion weighted imaging. The patient experienced no further episodes in hospital, and was discharged home on phenytoin and clonidine.

The patient returned two weeks later complaining of dysarthria, ongoing paresthesias and intermittent low amplitude twitching of the left face. Examination revealed mild dysarthria and subtle irregular

twitching of the left facial muscles including masseter, orbicularis oris and platysma, with sparing of the forehead. Repeat MRI revealed extension of the lesion in the right temporoparietal region. Gyriform T1 hyperintensity was identified with underlying T2 hyperintensity in the subcortical white matter (Figure 1). There was little associated mass effect and minimal regional sulcal effacement. Repeat CSF examination revealed an elevated WBC count of $23/\text{mm}^3$ with a predominance of lymphocytes. Antibodies to glutamate receptor R3 were not detected in the CSF. Repeat EEG showed ongoing periodic lateralized epileptiform discharges. An angiogram of the cerebral vessels was normal.

Over the next several weeks the patient developed continuous, irregular, large amplitude myoclonic movements of the left face at 5-10 Hz. Eventually the right face became involved, although to a lesser extent than the left. The patient also developed twitching of the tongue and palate, characterized by irregular large amplitude and high frequency jerks synchronous with those of the left face. Consciousness and cognition were not measurably impaired at this point. However, the patient lost the ability to speak and had significant incoordination of

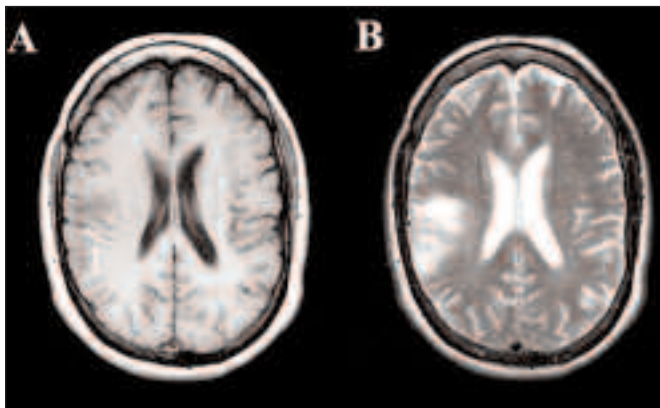


Figure 1: (A) Axial T1 weighted MRI demonstrates hypointense signal in the right temporoparietal region with cortical gyriform hyperintense signal (arrow). (B) T2 weighted MRI demonstrates hyperintense signal in the corresponding region.

swallowing, but was able to communicate effectively by writing. Several anticonvulsant medications were administered with very limited response.

The patient then experienced insidious onset of deficits in cognition, attention, and visuospatial reasoning. The patient was unable to form simple mathematics, tended to perseverate, and lost the ability to communicate using handwriting. She was unable to ambulate or sit upright independently. Frequent episodes of unresponsiveness and staring developed. There was no evidence of neglect. (deletion).

Biopsy of the right temporoparietal region revealed diffuse astrocytic gliosis (Figure 2) and microglial activation, with microglial and neuronophagic nodules in the cortex (Figure 3), and occasional microglial nodules in subcortical white matter. Perivascular lymphocytic cuffing was present in the cortex, and to a lesser extent in the leptomeninges and subcortical white matter (Figure 4). Scattered

intraparenchymal and leptomeningeal lymphocytes were also present. Perivascular and leptomeningeal lymphocytes consisted of CD3 immunopositive T cells and CD20 immunopositive B cells, while intraparenchymal lymphocytes were predominantly T cells. Intracellular viral inclusions were not identified, and immunohistochemistry was negative for CMV and HSV1 and 2, as was in-situ hybridization for EBV.

A diagnosis of Rasmussen's encephalitis was made and a course of intravenous immunoglobulin was initiated. There was marked improvement over the next several weeks following just four days of

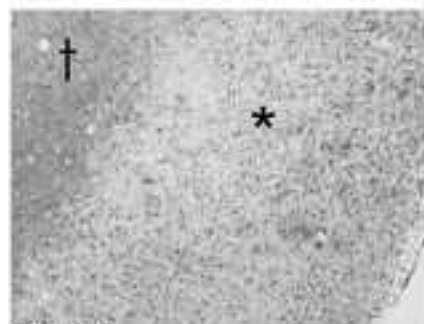


Figure 2

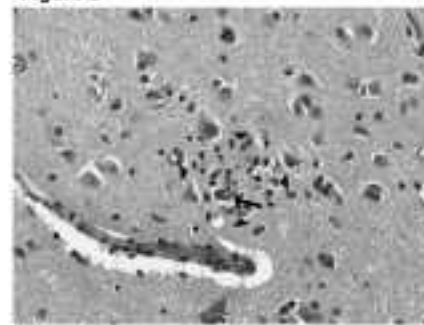


Figure 3

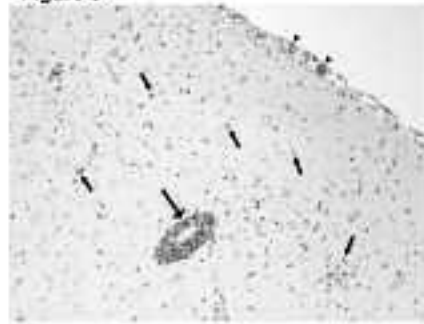


Figure 4

Figure 2: Diffuse astrocytic gliosis involving cortex (asterisk) and subcortical white matter (cross). (Dako GFAP immunoperoxidase, DAB/haematoxylin; original magnification $\times 40$)

Figure 3: Neuronophagic nodule in cortex (arrowheads). Arrow points to neuron. (H&E; original magnification $\times 400$).

Figure 4: Perivascular lymphocytic cuff (large arrow) and scattered intraparenchymal (small arrows) and leptomeningeal (arrowheads) lymphocytes. (NeoMarkers CD3 immunoperoxidase, DAB/haematoxylin; original magnification $\times 100$).

IVIg therapy, both with respect to cognition and seizure activity. The patient was again able to speak after several weeks of very limited communication by handwriting and gestures. Treatment was complicated by a deep venous thrombosis and anemia with a positive coomb's test, and treatment was stopped after eight days (deletion). The patient continued to improve symptomatically and functionally for approximately 14 days, after which her condition was stable for an additional week. At this time, slow progression of deficits returned with increased weakness and jerking of the left hand and face as well as palate with loss of comprehensible speech. There was no improvement with a course of plasmapheresis. After placement of an inferior vena cava filter, IVIG was resumed with weekly 2-day courses, which resulted in moderate improvement in cognition, speech and seizure activity. At a one year follow-up visit, with ongoing treatment, the patient was living independently, ambulating unassisted, and seizure free with minimal cognitive impairment. She had, however, developed neglect and astereognosis of the left hand. At 18 months, the patient was demonstrating some clinical evidence of focal seizures affecting the left face although functionally and cognitively was stable. Neglect and astereognosis had resolved.

DISCUSSION

This patient represents the oldest confirmed case of Rasmussen's encephalitis and adds to the growing body of evidence suggesting that the adult variant is more common than previously thought. Rasmussen's encephalitis should therefore be included in the differential diagnosis for any patient with chronic, progressive, focal encephalitis, particularly when characterized by epilepsy partialis continua. This case also poses important questions with respect to management of this disease in adults. While hemispherectomy is the standard of care for this condition in children, this may not be as suitable for adults, in whom cerebral functional plasticity is more limited. In patients with refractory seizures who are poor candidates for surgical intervention, the benefits of IVIG have been clearly demonstrated,^{4,6,7} and are further supported by the dramatic improvements seen in our patient. We therefore propose that IVIG be employed as a first line agent in the treatment of adult onset RE.

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