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Clinical Observations

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis and Rasmussen-like Syndrome: An Association?

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ABSTRACT

BACKGROUND: *N*-methyl-D-aspartate (NMDA) receptor encephalitis is an immune-mediated condition that has a broad spectrum of manifestations, including seizures, coma, psychosis, and focal neurological deficits. Although usually a diffuse process, unihemispheric involvement mimicking early stages of Rasmussen encephalitis can occur. Rasmussen's encephalitis is a unique syndrome characterized by progressive hemiplegia, drug-resistant focal epilepsy, cognitive decline, and hemispheric brain atrophy contralateral to the hemiplegia. **PATIENT DESCRIPTION:** We describe a two-year-old girl with progressive right weakness and epilepsia partialis continua, concerning for early Rasmussen's encephalitis, who tested positive for anti-NMDA receptor antibodies. She experienced complete clinical recovery after immunotherapy. Anti-NMDA receptor antibodies were absent at three weeks and again at one year after the first treatment of intravenous immunoglobulin. **CONCLUSIONS:** There are few reports of Rasmussen-like encephalitis in individuals with anti-NMDA receptor antibody positivity. Thus the clinical significance of this association is yet to be determined. In addition, several other antibodies have been documented in individuals with Rasmussen encephalitis. The lack of a consistently reported antibody in Rasmussen encephalitis patients and the temporary nature of the anti-NMDA receptor antibody in our patient raise the following question: Is the presence of anti-NMDA receptor antibodies the cause of the symptoms or secondary to the pathogenic process?

Keywords: Rasmussen syndrome, NMDA receptor, AMPA receptor, glutamate, encephalitis, pediatrics, autoimmune

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Patient Description

This previously normal two-year-old girl developed subacute onset of progressive right hemiparesis, speech regression, and right body focal seizures described as frequent right arm or leg twitching. Electroencephalography (EEG) showed continuous delta rhythm in the left hemisphere (Fig 1). Numerous right-sided twitching episodes were captured on EEG without any clear ictal change. Seizures remained refractory to oxcarbazepine and levetiracetam. Her contrast-enhanced brain magnetic resonance imaging (MRI) was normal. The possibility of stage I Rasmussen encephalitis was suggested by her clinical presentation, and a positron emission tomography (PET) study was performed, which demonstrated diffuse left hemispheric hypermetabolism (Fig 2).

Given the clinical picture and PET findings, the child was readmitted to the hospital for further autoimmune evaluation and immune therapy. Cerebrospinal fluid (CSF) was submitted for the following studies: chemistry, glutamate receptor 3 (GluR3) antibody, *N*-methyl-D-aspartate receptor (NMDAR) antibody, cytology, flow cytometry, oligoclonal bands, myelin basic protein, Immunoglobulin G index, electrophoresis, and a viral panel. In addition, serum NMDAR antibody was submitted. Once these studies were submitted, intravenous immunoglobulin (IVIG) was started; dosing was 2 g/kg divided over five days.

Unfortunately, there was not enough CSF to perform the GluR3 and NMDA studies. The other CSF studies were normal. The serum NMDAR antibody study was positive, however. The serum NMDAR antibody titer value was not available. Abdominal and pelvic ultrasound examinations did not reveal an ovarian teratoma.

When she was seen for follow-up three weeks later, her speech had improved and she was using her right side more. She still had occasional twitching of the right side. Physical examination was notable for increased tone of the right upper extremity, a mild right pronator drift, and decreased speed of rapid alternating movements on the right. Serum anti-NMDA receptor antibody was resent and MRI was repeated. The

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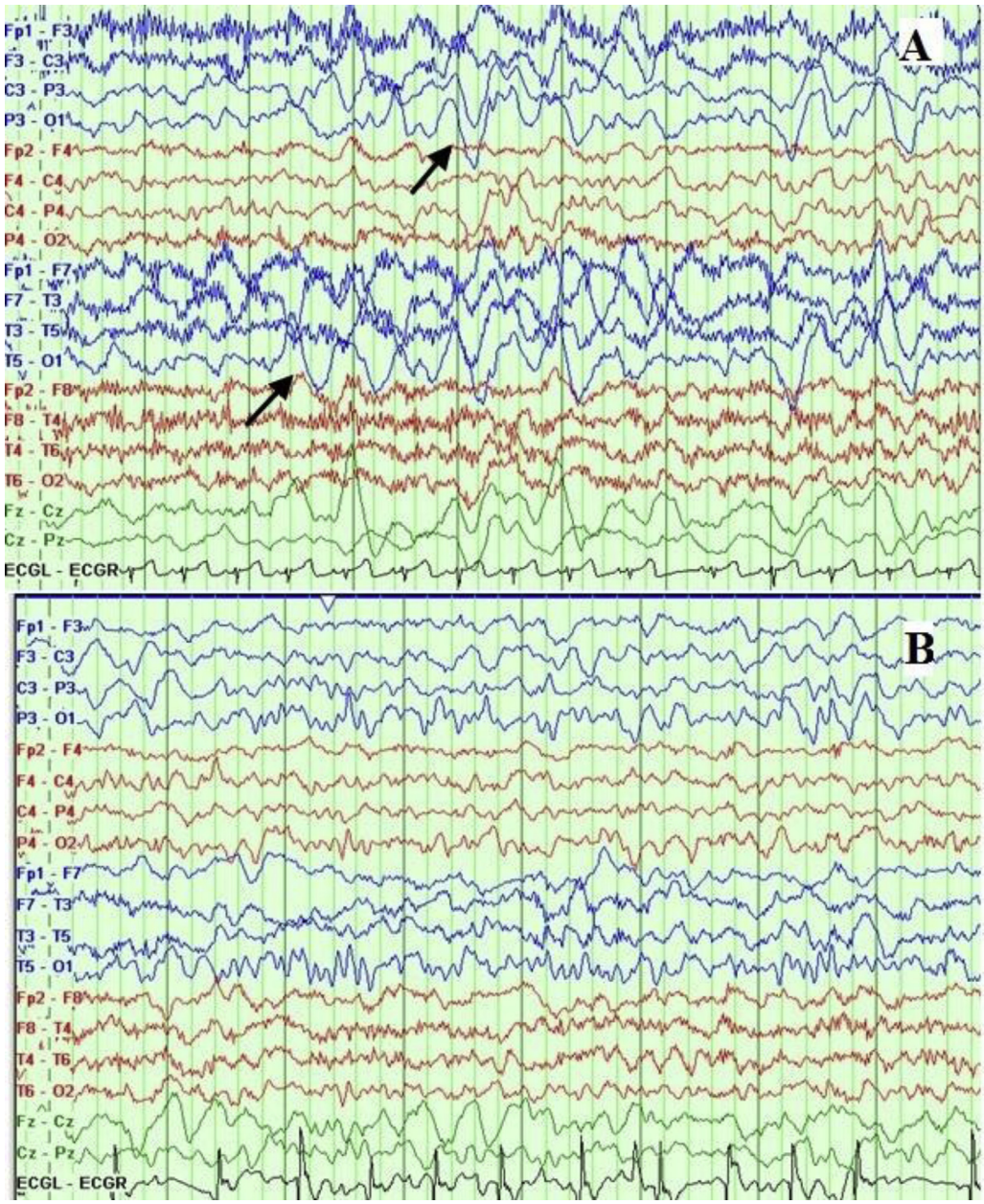

FIGURE 1.
(A) Initial EEG at the time of presentation showing left-sided slowing (black arrows). (B) EEG after six months of treatment with intravenous immunoglobulin documents resolution of the slowing. (The color version of this figure is available in the online edition.)

repeat NMDA receptor antibody was negative. Brain MRI showed no atrophy but had areas of increased cortical thickness within the left frontal, parietal, and temporal lobes on fluid-attenuated inversion recovery (FLAIR) sequence (Fig 3). Repeat EEG continued to show left slowing. The decision was made to continue IVIG 2 g/kg every four to five weeks for one year.

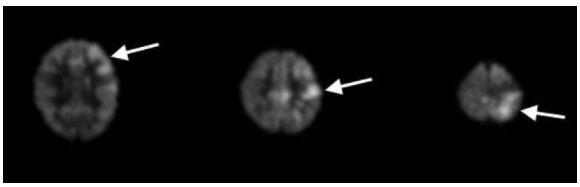

FIGURE 2.
Positron emission tomography—documents increased fludeoxyglucose uptake (white arrows) involving the left temporal and frontal lobes.

Her speech rapidly improved and was normal by three months after the initial treatment. Her weakness improved more slowly than her speech, but it too was normal seven to eight months after initial treatment. Body twitching episodes had resolved four months after the initial treatment. Her parents self-discontinued antiepileptic drugs eight months after the initial treatment. Her EEG had normalized ten months after the initial IVIG treatment. A serum anti-NMDA receptor antibody was sent for a third time 11 months after treatment and it was unremarkable. Pelvic and abdominal ultrasound at 12 months was normal. In total she received six doses of IVIG. Now more than three years after her initial IVIG treatment, she remains asymptomatic with normal developmental milestones in accordance with the Denver II Developmental screening checklist.

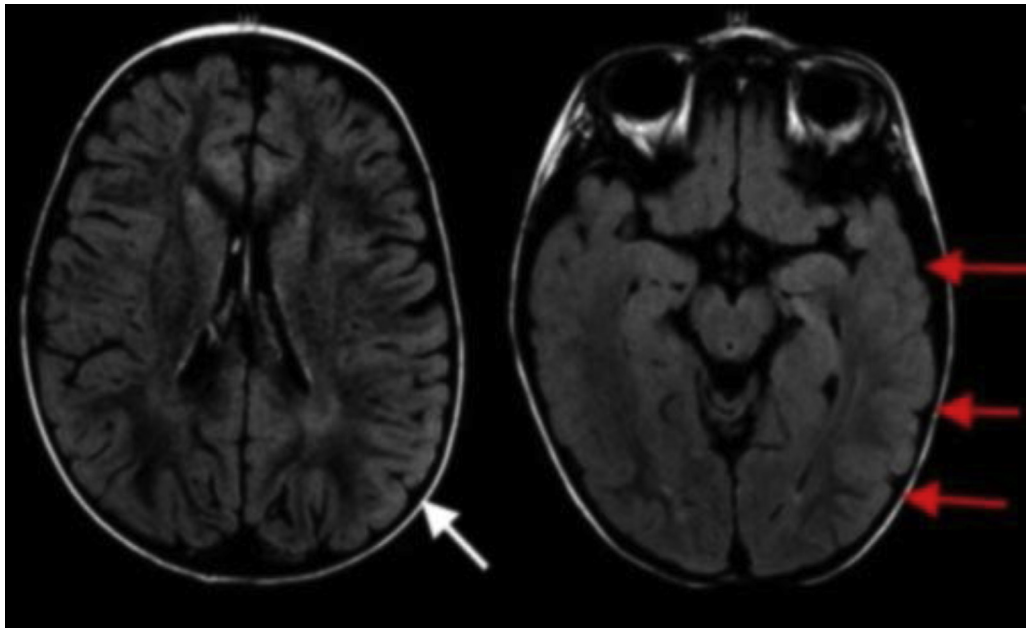

FIGURE 3.
MRI T2 —FLAIR sequence reveals increased signal (white arrow) in the left frontal, parietal, and temporal lobes with mild thickening (red arrows) of the cortex compared with the right side. (The color version of this figure is available in the online edition.)

Discussion

The diagnosis of Rasmussen encephalitis is based on Bien criteria.[1] Our patient met two thirds of the "A" criteria (clinical—unilateral cortical deficits, EEG) and had abnormal FLAIR signal but lacked atrophy (it may have been too early in the disease course for this finding to occur). In addition, our patient met one third of the "B" criteria (progressive unicortical deficits). Refinement of Bien criteria has been recommended because Rasmussen encephalitis can have a variable clinical presentation and findings like MRI atrophy evolve over time.[2] PET findings in individuals with Rasmussen encephalitis have not been thoroughly studied but potentially could be used to make an earlier diagnosis. Although this child did not have a biopsy and cannot be confirmed as definite Rasmussen encephalitis, her progressive cortical deficits, which worsened rapidly in a short period of time, were suggestive of a Rasmussen encephalitis-like disease process.

The spectrum of NMDA receptor antibody encephalitis is expanding rapidly, particularly in pediatric patients. A review of the literature identified another 11-year-old girl presenting with a Rasmussen encephalitis-like syndrome whose CSF was positive for NMDA receptor antibodies and response to immunotherapy.[3] Six months later, an ovarian teratoma was identified.

A 2005 study documented the presence of NMDA glutamate 2 (GluN2) subunit receptors in individuals with Rasmussen encephalitis.[4] The diagnosis was proven by biopsy in nine of the 20 patients. All but one patient had either serum or CSF for antibodies to the GluN2 subunits.

On the other hand, a 2016 study examined alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (AMPAR) antibodies in Rasmussen encephalitis.[5] Sera from 52 individuals with Rasmussen encephalitis were tested by cell-based assays for antibodies to AMPAR GluA1/2/3, NMDA NR1/2b, γ-aminobutyric acid type A and B (GABAAR α1/γ2/β2 and GABABR b1/b2) receptors, for potassium channel complex proteins, and for binding to live cortical and hippocampal neuronal cultures. Interestingly, two patients were positive for both AMPAR GluA2 and 3, one patient was positive for voltage-gated potassium channel, and seven patients were positive for sera bound to hippocampal cultures. None of the patients tested positive for NMDA receptor antibodies.

What these studies and our patient illustrate is that the specificity of a particular antibody to Rasmussen encephalitis has yet to be established. Despite this heterogeneity, it is apparent that there is an inflammatory component to the disease process. One unifying factor of the NMDAR and AMPAR is that they are subtypes of ionotropic glutamate receptors. Perhaps, broadly speaking, disruption of glutamate receptors may be the root cause. Future studies are needed to further elucidate the significance of antibodies with respect to pathogenesis.

A study of patients with clinically diagnosed Rasmussen encephalitis examined the presence of NMDA type glutamate 1 (GluN1) and 2b (GluN2b) receptors in the CSF.[6] The patients were studied during four time periods measured from the onset of epilepsy: less than 11, 12 to 23, 24 to 47, and more than 48 months. Seven of ten patients tested positive for GluN2b and five of 10 were positive for GluN1 at 12 to 23 months. The percentage decreased significantly after 24 months for both receptors. Anti-GluN2b antibody levels in CSF sampled when seizures occurred daily were significantly higher than those when seizures occurred less frequently (defined as weekly, monthly, or seizure free). This finding shows that a high percentage of Rasmussen encephalitis patients tested positive for NMDAR antibodies

during the disease course, with the peak incidence at a similar time and the highest amount of antibody during its most active clinical phase. Although the sample size is small, these findings suggests the antibody could be a marker for active inflammation. Our patient was about one month into her disease course when the NMDA receptor antibody tested positive.

Our patient had a positive serum NMDA receptor antibody and had many features of Rasmussen encephalitis but did not meet the diagnostic criteria. It would have been interesting to see if other antibodies would have been positive. Her NMDA receptor antibody was absent three weeks after treatment. This child's findings suggest intriguing questions: was the NMDA receptor antibody causative and the immunotherapy altered the disease course with excellent outcome, or was it merely represents a marker of neuroinflammation secondary to seizures or encephalitis? Our patient also underscores the importance of considering other possible diagnoses during the evaluation.

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