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The Enemy Within: Anti-N-Methyl D-Aspartate Receptor Encephalitis

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PRESENTATION

A 31-year-old woman presented as a transfer from an outside hospital for the evaluation of progressive altered mental status. She had been in good health until 1 month previously when she began to experience intermittent dizziness and headaches. This was followed by behavioral changes (erratic crying and laughing) and new seizure-like activity, which included eye rolling and whole-body shaking associated with urinary incontinence and postictal confusion. She became noncommunicative the week before transfer. Workup at the outside facility included a reportedly unremarkable lumbar puncture, computed tomography scan of the head, magnetic resonance imaging of the brain, magnetic resonance angiography of the brain and neck, and electroencephalogram. After this negative workup, valproic acid was administered and she was transferred to an inpatient psychiatric facility where she had progressive catatonia, seizure-like activity, and hypothermia. She was then transferred to Tama General Hospital for further care. On admission, she was unable to provide a history. She had intermittent agitation and outbursts of crying, laughing, and screaming, as well as choreiform movements of the face consisting of twitching, teeth grinding, and lip smacking.

ASSESSMENT

On examination, she had a blood pressure of 105/72 mm Hg, heart rate of 102 beats/min, and temperature of 93.5°F (34.2°C). She was awake and alert, but nonverbal and not following commands. Her eyes would open to voice and track movement. Pupils were equal and responsive to light and accommodation. There was no nystagmus or gross facial weakness. She did not blink to threat, but had intact corneal, gag, and cough reflexes. She did not withdraw to pain. Muscle tone was normal without atrophy, rigidity, or spasticity. Deep tendon reflexes were 2+ throughout, and she had an upward left plantar reflex.

Complete blood count and comprehensive metabolic panel were notable for a leukocyte count of 16.6×10^3 cells/μL with neutrophil predominance, aspartate aminotransferase of 50 IU/L, and alanine aminotransferase of 114 IU/L. Magnetic resonance imaging of the brain revealed 2 areas of hyperintensity on fluid-attenuated inversion recovery images abutting the posterior horn of the right ventricle and the fourth ventricle, possibly representing demyelinating disease, vasculitis, or atypical infection (**Figure 1**). Continuous electroencephalography (EEG) demonstrated diffuse slowing and intermittent generalized delta activity with superimposed beta frequency activity (**Figure 2**). Seizure-like movements did not have epileptiform changes on EEG.

Autoimmune workup, including rheumatoid factor and anti-neutrophil cytoplasmic antibody, was negative. C-reactive protein was 3.96 mg/dL (reference range, <0.5 mg/dL) and erythrocyte sedimentation rate was 97 mm/h (reference range, <20 mm/h). Human immunodeficiency virus test results were negative. She was found to be positive for hepatitis B core total antibody and surface antibody. Hepatitis B surface antigen was negative, and viral load was undetectable. Further laboratory assessment revealed elevated antithyroid microsomal antibodies 148.6 IU/mL (reference range, <5.6 IU/mL) with a normal thyroid-stimulating hormone and free T4. Cerebrospinal fluid demonstrated 128 nucleated cells/μL with 86% lymphocytes. Cerebrospinal fluid protein was 56 mg/dL (reference range, 15-45 mg/dL). Multiple oligoclonal bands (>5) were present. Bacterial, fungal, and viral cerebrospinal fluid studies were negative. Anti-N-methyl D-aspartate (NMDA) receptor antibodies were detected.

DIAGNOSIS

The patient was diagnosed with anti-NMDA receptor encephalitis. First described in 2007, anti-NMDA receptor

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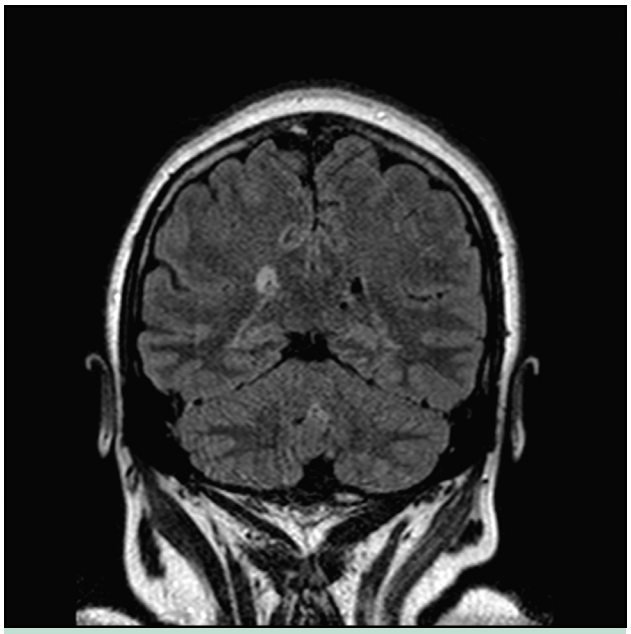

Figure 1 Magnetic resonance imaging of the brain reveals an area of hyperintensity abutting the right ventricle visualized on coronal fluid-attenuated inversion recovery image.

encephalitis is a relatively new clinical phenomenon and initially described as a paraneoplastic encephalitis associated with ovarian teratomas.[1] The triggers leading to autoantibody formation remain unclear, but paraneoplastic, postinfectious, and autoimmune triggers have been described.[2,3] Patients typically present with a prodrome of headache, fever, fatigue, and alterations of body temperature suggestive of a flu-like illness. This is then followed by neuropsychiatric symptoms: agitation, short-term memory loss, orofacial twitching and other choreoathetosis often mistaken for seizure activity, delusions, hallucinations, mood disturbances, and dissociative responses to stimuli.[3,4] Symptoms can progress to include autonomic instability and hypoventilation.

The definitive diagnosis of anti-NMDA receptor encephalitis requires the detection of antibodies to the NMDA receptor in the serum or cerebrospinal fluid in the appropriate clinical setting. Magnetic resonance imaging may reveal transient fluid-attenuated inversion recovery abnormalities, but is normal in approximately 50% of patients.[5,6] EEG typically shows nonspecific slowing, but epileptic activity may be seen in approximately 20% of cases.[4-6] A recently described EEG pattern termed "extreme delta brush," which consists of generalized rhythmic delta activity with superimposed beta frequency activity, may be seen in a subset of patients and is considered highly specific of the disease.[7]

Although approximately 59% of cases are associated with an ovarian teratoma, other paraneoplastic associations include sex-cord stromal tumors, neuroendocrine tumors, mediastinal teratomas, small-cell lung cancer, and testicular germ-line tumors.[5] Infectious associations have been described in cases of *Mycoplasma pneumoniae*, influenza

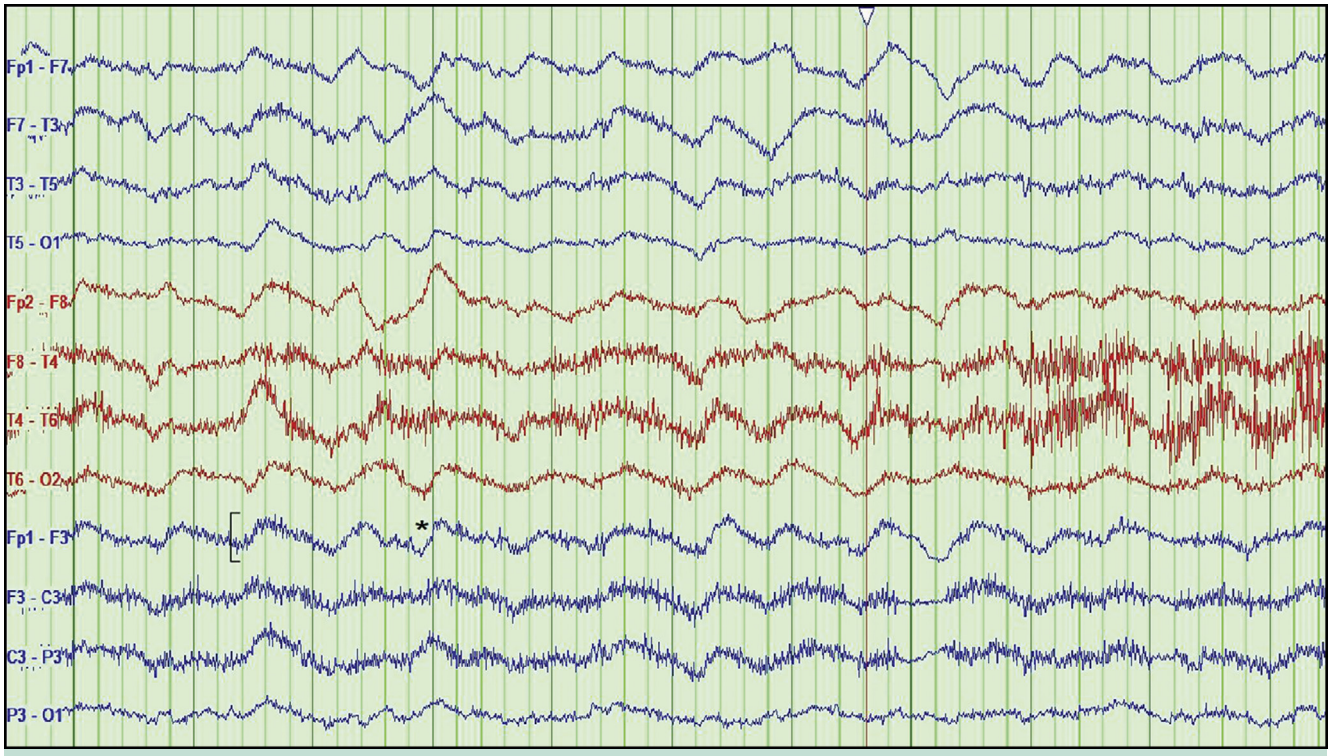

Figure 2 EEG tracing demonstrates generalized rhythmic delta frequency (bracket) with superimposed low-amplitude beta frequency activity (*).

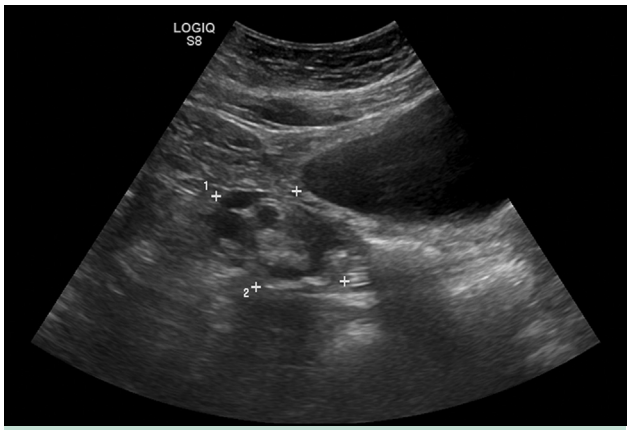

Figure 3 Transvaginal ultrasound shows a right adnexal mass.

virus A and B, *Chlamydia pneumoniae*, *Bordetella pertussis*, and Epstein-Barr virus.[3,8] Positive hepatitis B serology has not previously been reported. Antithyroid antibodies, classically associated with Hashimoto's encephalopathy, have been identified in a few cases without an associated tumor and only 1 case with an associated teratoma.[2,8,9] The pathogenesis of anti-NMDA receptor encephalitis appears to be multifactorial in nature, and our understanding of it is rapidly evolving.

MANAGEMENT

Treatment modalities in anti-NMDA receptor encephalitis are based on case reports and series, and the mainstay approach consists of immunotherapy along with tumor removal if present. On diagnosis, all patients should be assessed for ovarian teratoma or testicular germ-cell tumor.[6] Tumor removal results in a higher likelihood of response to first-line treatment and lower likelihood of relapse.[4,6,10] First-line immunotherapy consists of corticosteroids, intravenous immunoglobulin, or plasma exchange. The use of these agents alone or in combination, along with tumor removal, results in substantial clinical improvement in the majority of patients.[6] Those without a paraneoplastic association respond to first-line therapy less frequently, and often require treatment with second-line agents, rituximab, or cyclophosphamide.[4,6,10]

During the diagnostic process, our patient was started on high-dose methylprednisolone and subsequent intravenous immunoglobulin without improvement. After detection of anti-NMDA receptor antibodies, a subsequent pelvic ultrasound revealed a right adnexal mass. The 5.4 × 6.0 × 4.1-cm heterogeneous, hyperechoic complex cystic mass without vascularity appeared consistent with an ovarian teratoma (**Figure 3**). Surgical resection confirmed the mature cystic teratoma. Secondary to her persistent symptoms, rituximab was initiated 8 days after surgery. This resulted in a rapid and dramatic improvement in her neurologic status. She was able to follow commands and speak within the first week of starting treatment. After completing weekly cycles of rituximab for 1 month, she regained strength in all of her extremities, completed a rehabilitation program, and returned to her baseline mental function.

CONCLUSIONS

Anti-NMDA receptor encephalitis should be considered in any patient presenting with the rapid onset of behavioral changes accompanied by unusual movements or postures, seizures, and autonomic instability, especially in the absence of an obvious infectious or metabolic cause.

References

1. Dalmau J, Tuzun E, Wu H, et al. Paraneoplastic anti−N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61:25-36.
2. Guan W, Fu Z, Zhang H, et al. Non-tumor-associated anti-N-methyl-D-aspartate (NMDA) receptor encephalitis in Chinese girls with positive anti-thyroid antibodies. *J Child Neurol*. 2015;30:1582-1585.
3. Peery HE, Day GS, Dunn S, et al. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. *Autoimmun Rev*. 2012;11:863-872.
4. Barry H, Byrne S, Barrett E, et al. Anti-N-methyl-D-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. *BJPsych Bull*. 2015;39:19-23.
5. Dalmau J, Gleichman A, Hughes E, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7:1091-1098.
6. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63-74.
7. Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush, a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology*. 2012;79:1094-1100.
8. Pruss H, Dalmau J, Harms L, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology*. 2010;75:1735-1739.
9. Xu CL, Liu L, Zhao W, et al. Anti-N-methyl-D-aspartate receptor encephalitis with serum anti-thyroid antibodies and IgM antibodies against Epstein-Barr virus viral capsid antigen: a case report and one year follow-up. *BMC Neurol*. 2011;11:149.
10. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12:157-165.