CHEST Postgraduate Education Corner
PULMONARY, CRITICAL CARE, AND SLEEP PEARLS

A 35-Year-Old Woman With Unusual Behavior and Prolonged Respiratory Failure

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A 35-year-old woman was brought to the ED by family members with a 3-day history of behavioral changes. The patient exhibited confusion, confabulation, and occasional combativeness. Her family denied any recent flu-like symptoms, sick contacts, or recent travels. Her medical history was significant for mild intermittent asthma. The patient had no history of psychiatric illness. Her medications included occasional albuterol use for well-controlled asthma. She worked as a registered nurse and was married with three children. She smoked one-half a pack of cigarettes a day and drank alcohol occasionally. According to her husband, the patient had a remote history of inhalational cocaine use and recent tattoos but no history of IV drug use.

Physical Examination Findings

The patient's temperature was 101.5°F; BP, 147/95 mm Hg; pulse, 116 beats/min; respiratory rate, 24 breaths/min; and oxygen saturation, 99% on room air. In general, the patient was a young woman of medium build and appeared to be confused and agitated. No head or neck trauma or meningismus were observed. Her chest was clear on auscultation bilaterally. She had normal S1 and S2 sounds and no murmurs. Her abdomen was soft and nontender with no hepatosplenomegaly. The patient was awake but not oriented, mumbling, agitated, and combative. Her pupils were equal and reactive to light; no nystagmus was noted. The patient could move all four extremities and had normal reflexes, and no clonus was present. There were no skin rashes, and a well-healed tattoo was noted on the lateral aspect of her right ankle.

Diagnostic Studies

Laboratory tests showed a WBC count of 15,400/mL with 83% neutrophils and serum hematocrit level of 38.3% with a mean corpuscular volume of 91.7 fL. Serum electrolyte values were as follows: sodium, 139 mEq/L; potassium, 4.2 mEq/L; chloride, 102 mEq/L; bicarbonate, 23 mmol/L, BUN, 12 mg/dL; creatinine, 0.9 mg/dL; glucose, 93 mg/dL; calcium, 9.3 mg/dL; magnesium, 1.9 mEq/L; and phosphorus, 4.0 mEq/L. Urine toxicology results were negative. Cerebrospinal fluid (CSF) analysis was notable for a WBC count of 93/mm^3, with 91% lymphocytes and normal protein and glucose levels. Chest radiograph revealed no acute pulmonary disease. Brain MRI revealed T2 hyperintensity in the bilateral hippocampi (Fig 1).

The patient was treated empirically for bacterial and viral meningitis but worsening confusion and agitation developed. Periodic choreoathetoid movements of the face and extremities were noted over the next few days. On hospital day 8, she was found to be comatose, with agonal breathing and diffuse rhonchi bilaterally. Blood gas analysis revealed a pH of 7.40, $PaCO_2$ of 50 mm Hg, and PaO_2 of 40 mm Hg. She was intubated for presumed aspiration and hypoxemic respiratory failure and transferred to the ICU. EEG at the time revealed epileptic activity consistent with nonconvulsive status epilepticus. A repeat chest radiograph showed no new pulmonary opacities. High doses of opioids and benzodiazepines were required to control agitation and orofacial dyskinetic movements. Over the following days, multiple trials at extubation were unsuccessful secondary to a depressed mental status and severe tachypnea. Tracheostomy was performed on day 18.

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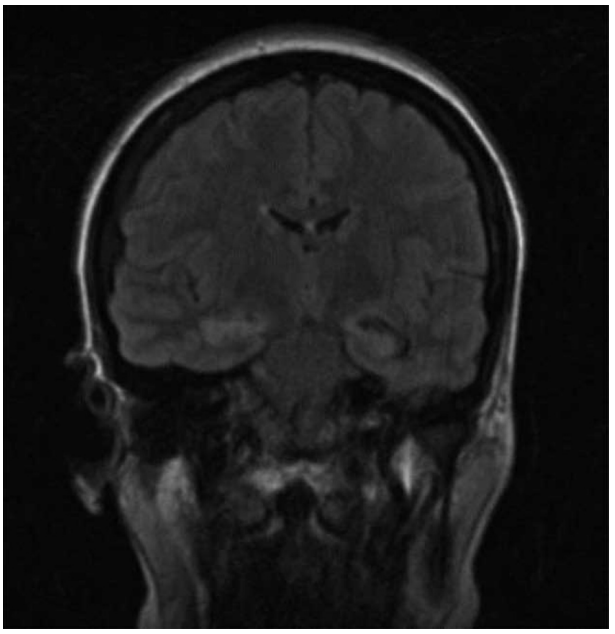

FIGURE 1. Coronal T2 fluid-attenuated inversion recovery images on MRI of brain revealing dominant hyperintensity in bilateral hippocampi.

Bacterial, fungal, viral, and acid-fast bacillus cultures of blood and CSF were negative. Serologic studies for *Legionella*, Lyme disease, syphilis, toxoplasmosis, *Cryptococcus*, HIV, cytomegalovirus, Epstein-Barr virus, West Nile virus, measles, adenovirus, herpes simplex virus 1/2, varicella-zoster virus, human herpesvirus 6, and enterovirus were negative. Laboratory studies for connective tissue diseases were negative. Antibodies to CA125, Purkinje cell, and antineuronal nuclear antibody (anti-Hu/anti-Ri) were negative. A whole-body CT scan was unremarkable except for a 1.2-cm cyst on the left ovary. During the fourth week of hospitalization, antibodies to the *N*-methyl-D-aspartate (NMDA) receptor were detected in the serum and CSF.

What is the diagnosis?

Discussion

Anti-NMDA receptor encephalitis (ANRE) is a severe type of autoimmune paraneoplastic encephalitis first identified in 2007. It is a rare disorder associated with antibodies to NR1-NR2 heteromers of the NMDA receptor. NMDA receptors are ligand-gated cation channels that play important roles in synaptic transmission and plasticity, a mechanism for memory and learning. Overactivity of NMDA receptors is believed to be a mechanism for epilepsy, dementia, and stroke, whereas low activity leads to symptoms of schizophrenia. Antibodies to the NR1-NR2 subunits cause a characteristic schizophrenia-like neuropsychiatric syndrome.

Up to 90% of patients with ANRE are young women (median age, 23 years). Patients typically present with psychiatric symptoms, such as behavioral changes, agitation, psychosis, and hallucinations, and progress rapidly to decreased responsiveness and central hypoventilation. Other characteristic features are catatonia, dyskinesia, autonomic instability, seizures, and persistent amnesia. In fact, the majority of patients exhibit seizure activity, unresponsiveness, and central hypoventilation, leading to respiratory failure, as seen in the present patient. Patients frequently require ICU management and prolonged ventilatory support. In a case series, the median time required for ventilatory support is around 8 weeks and can range anywhere from 2 to 40 weeks. Although the association with viral infections is uncertain, prodromal viral-like symptoms are observed in the majority of cases.

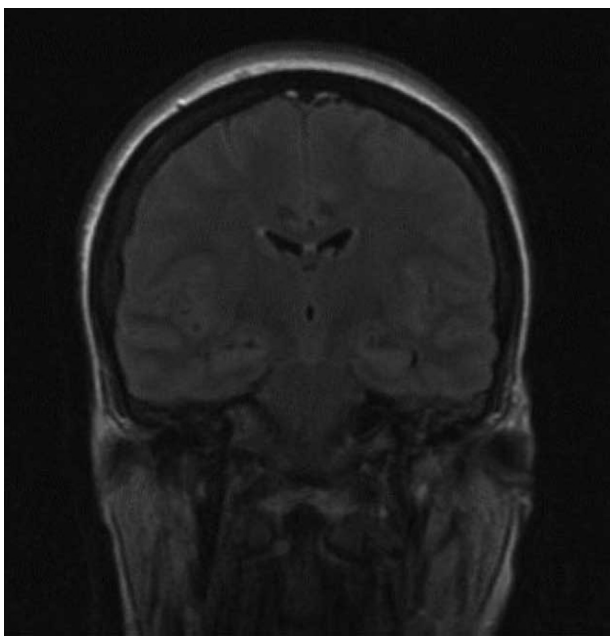

Figure 2. MRI of brain showing partial resolution of bilateral hippocampal hyperintensity after steroid therapy.

CSF analysis shows lymphocytic pleocytosis and increased protein concentration. Brain MRI is usually nonspecific and can include increased fluid-attenuated inversion recovery or T2 enhancement in one or several regions; however, any significant correlation to the patient's symptoms is lacking. EEG commonly shows nonspecific diffuse slowing without epileptic discharges. Only the detection of the anti-NMDA receptor antibodies in CSF and serum is diagnostic for ANRE.

Tumors are found in up to 59% of patients, most commonly ovarian teratoma. Men and children can rarely be affected and have been reported to have testicular teratomas. Up to 75% of patients attain either full recovery or recovery with mild deficits with removal of the teratoma. Early detection and removal of the tumor is strongly associated with earlier and higher rates of neurologic recovery and fewer relapses. The teratoma almost invariably has ectopic neural tissue. Up to 40% of patients with ANRE do not have a clinically detectable tumor, which confers a worse prognosis. Patients may respond to immunotherapy, such as corticosteroids, plasma exchange, IV immunoglobulin, cyclophosphamide, and rituximab, but tumor detection and removal offer the best chance of recovery. Interestingly, symptoms may precede the detection of a teratoma by years; hence, a thorough oncologic assessment with ultrasound, CT scan, or MRI is necessary. Low serum titers of NMDA receptor antibodies after treatment are associated with a better prognosis. Recovery from this disorder typically is slow, and symptoms may relapse years later, especially in patients with initially undetected or recurrent tumors and those with no tumor association.

Clinical Course

A paraneoplastic encephalitis was suspected because of the lack of clinical improvement with supportive therapy, and hence, CT scan of the chest, abdomen, and pelvis was performed to evaluate for tumor. On detection of anti-NMDA receptor antibodies, pulse-dose corticosteroids were administered at 1 g daily for 5 days, with only minimal clinical response and minimal resolution of T2 hyperintensity on follow-up MRI (Fig 2). A transvaginal ultrasound confirmed a complicated cyst in the left ovary. A left-side salpingo-oophorectomy was subsequently performed, leading to a dramatic improvement in the patient's mental status and neuromuscular function within 2 days of surgery. Pathology revealed mature cystic teratoma containing neural tissue. The patient was liberated

from the ventilator < 1 week after teratoma removal. She became fully communicative and ambulatory and was discharged to acute rehabilitation services after a total 2-month hospitalization. On 1-year follow-up, the patient had near full neurologic recovery but had been unable to return to work because of residual mild memory impairment.

Clinical Pearls

1. ANRE is a newly described severe form of encephalitis associated with antibodies against NR1-NR2 heteromers of the NMDA receptor.

2. ANRE should be suspected in young women with encephalitis of unknown etiology who present with psychiatric symptoms.

3. Diagnosis is made by the detection of the anti-NMDA receptor antibodies in CSF and serum.

4. Immunotherapy and a comprehensive assessment for occult teratoma with subsequent removal of tumor result in significant improvement in neurologic outcomes.

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Suggested Readings

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