case report

Anti-NMDA-receptor encephalitis presenting as postpartum psychosis in a young woman, treated with rituximab

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A severe paraneoplastic form of acute encephalitis associated with antibodies against the N-methyl D-aspartate (NMDA) receptor typically occurs in young individuals and is associated, but not always, with an underlying tumor. If diagnosed early, initiation of immunotherapy and tumor removal (if present) may result in recovery. We report a case in a 25-year-old young woman who presented to our medical center with postpartum psychosis. Treatment with rituximab (a chimeric monoclonal antibody against the protein CD20) resulted in gradual improvement in mental status and resolution of seizure activity episodes. A year after diagnosis and treatment, the patient was doing well without recurrences, and no tumors appeared. This is the first described case of anti–NMDA-receptor antibodies encephalitis that presented initially as a postpartum psychosis disorder and was successfully treated with rituximab.

N-methyl D-aspartate (NMDA) receptors are ligand-gated cation channels whose function centers around synaptic transmission and plasticity.[1] The receptors are heteromers of NR1 subunits that bind glycine and NR2 (A, B, C, or D) subunits that bind glutamate. NR1 and NR2 combine to form receptor subtypes, and their pharmacological properties include localization and the ability to interact with intracellular messengers; they also have the ability to interact with intracellular messengers.[2] Hyperactivity of these NMDA receptors results in neuropsychiatric excitotoxicity, which can manifest clinically as epilepsy, dementia, and stroke; whereas hypoactivity produces symptoms of schizophrenia.[3] Anti-N-methyl-D-aspartate (anti-NMDA)-receptor encephalitis is a recently described neurological condition with antibodies against NR1-NR2 heteromers. It is composed of a well-defined set of clinical features that have been characterized in adults, frequently in young women, with teratomas of the ovary who develop changes of mood, behavior, and personality, resembling acute psychosis.[4] The clinical picture usually progresses to include seizures, a decreased level of consciousness, dyskinesias, autonomic instability, and hypoventilation.[5] Removal of the teratoma, immunotherapy, plasma exchange, intravenous immunoglobulin (IVIG), and corticosteroids have resulted in clinical improvement regardless of the severity of the encephalitis. This is suggestive of an underlying autoimmune component to the pathogenesis.[6] We report a case of anti-NMDA-receptor encephalitis in a woman whose initial clinical presentation was that of acute postpartum psychosis.

CASE

A 25-year-old female with no significant medical history presented with bizarre behavior and recurrent seizures. She stated that 1 week prior to admission, she had a flu-like illness associated with rhinorrhea and generalized malaise. She had given birth by normal vaginal delivery to a healthy boy 2 months ago. She subsequently developed status epilepticus with generalized tonic-clonic activity, which was treated with lorazepam 4 mg and phenytoin 1000 mg intravenously. She developed hypoventilation and had to be intubated. Her vital signs were stable, and physical examination, routine hematologic, studies and urine toxicology screening provided normal results. The head computed tomography (CT) scan was unremarkable; the cerebrospinal fluid (CSF) analysis showed white blood cell count of 111 cells/mL (normal 0-3 cells/mL) [lym-

phocytes 95%], red blood cell 1 cell/mL (normal o); protein 61 mg/dL (normal 15-45 mg/dL); glucose 64 mg/dL (normal 50-80 mg/dl). Serum glucose was 111 mg/dL. The erythrocyte sedimentation rate was 75 millimeters/hour (normal 3-5 mm/hr); antinuclear antibody, negative; rapid human immunodeficiency virus enzyme-linked immunosorbent assay, negative; rapid plasma reagin and the Venereal Disease Research Laboratory test, were negative. Tests for Lyme disease, Epstein-Barr virus, and arboviruses were negative. An autoimmunity panel of tests (including, among others, anti-double-stranded DNA, thyroid peroxidase, and anti-neutrophil cytoplasmic antibodies) were negative. CT scans of the chest, abdomen, and pelvis; and a PET scan were all unremarkable. She also had an endoscopy with jejunal biopsy, which was negative for Tropheryma whippelii. Acyclovir 10 mg/kg body weight every 8 hours was started empirically for herpes simplex virus (HSV) encephalitis. The magnetic resonance imaging (MRI) of the brain was negative. An electroencephalogram (EEG) showed severe diffuse slowing consistent with a diffuse encephalopathic state with an absence of epileptiform activity. The patient was started on methylprednisolone 1 g IV daily. On the CSF analysis, the HSV polymerase chain reaction (PCR) was negative, and acyclovir was discontinued. Cytomegalovirus and West Nile PCR were also negative. The CSF anti-Ma and anti-voltage-gated potassium-channel antibodies were negative; however, the anti-NMDA-receptor antibodies were positive. The patient was started on plasmapharesis. One week later, there was no improvement; therefore, rituximab was added to the regimen. The patient's mental status gradually improved, and she became more alert and was weaned off the ventilator. She was discharged home on levetiracetam 500 mg twice daily; and 2 months later, her cognitive functions, memory, and results of neuropsychiatric evaluation were completely normal.

DISCUSSIONS

Anti-NMDA-receptor antibodies bind to the NR2B or NR2A subunits of NMDA receptor. NR2B binds glutamate and is avidly expressed in the hippocampal and forebrain neurons of humans. These antibodies inhibit NMDA receptors in presynaptic gamma-aminobutyric acid (GABA)ergic interneurons, resulting in reduced GABA release and disinhibition of postsynaptic glutamatergic transmission with excessive release of glutamate in the prefrontal/subcortical structures. The pathogenic role of these antibodies is further strengthened by their disappearance during clinical improvement.[7] Anti–NMDA-receptor encephalitis is a treatable paraneoplastic neurologic condition that predominantly affects young women. It is characterized by a constellation of symptoms, which include psychotic encephalopathy, seizures, and abnormal movements of the trunk and face, particularly in the form of jaw dystonia.[8] With progression of the disease, patients frequently become catatonic and unresponsive to verbal commands, and then they commonly begin to display hyperkinesias and lingual-facial-buccal dyskinesias, as well as hypoventilation.[9] Early recognition of the typical clinical presentation can increase the index of suspicion and facilitate early and prompt initiation of appropriate therapy. Prüss et al recommended that all young patients admitted to the intensive care unit with encephalitic signs (like psychiatric symptoms and seizures) be tested for anti-NMDA-receptor antibodies.[10] The analysis of CSF typically reveals pleocytosis, increased protein concentration, and a high IgG index.[11] EEGs occasionally show epileptiform abnormalities, but usually reveal only diffuse slowing of the brain waves.[12] Most cases (75%) have either normal or atypical brain MRI findings with mild abnormalities surrounding the medial temporal lobes, often with cortical enhancement. The brain MRI may show transient fluid-attenuated inversion recovery or contrast-enhancing abnormalities in the cortical (brain, cerebellum) or subcortical (hippocampus, basal ganglia, white matter) regions. Hybrid F-18 fluorodeoxyglucose positron emission tomography (PET) is particularly useful to screen for an associated tumor in the absence of brain MRI findings. Though encephalitis associated with NMDA-receptor antibodies is potentially fatal, there is typically rapid symptomatic relief with immunosuppressive therapy, and it resolves entirely with tumor removal.[13]

The ideal management of anti-NMDA-receptor encephalitis is tumor resection and immunotherapy. Patients with this disorder, however, usually require ventilatory support and intensive care for seizures and autonomic instability, which can delay tumor removal.[14] Treatment with methylprednisolone, plasma exchange, or IVIG might result in partial or complete amelioration of neurologic symptoms or in stabilization allowing resection, although the tumor could grow during the delay.[15] In some patients, tumor removal results in noticeable neurological improvement in a matter of days or after several weeks. Our patient, after diagnosis, was treated with plasma exchange, steroids, and IVIG with minimal improvement. Dramatic improvement was noted after initiation of rituximab. Patients (often, those without a tumor) who do not improve with typical first-line therapies may improve with rituximab and/or cyclophosphamide.[16]

Progressive neurologic deterioration and death can occur without treatment. However, spontaneous recovery has also been described in a few patients after several months of severe symptoms. Relapse occurs in 15% to 20% of the patients and is often associated with occult or relapsing teratoma or with the absence of a tumor.[17]

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