Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

Sian Y. Lim, MD, Ragesh Panikkath, MD, Charoen Mankongpaisarnrung, MD, Ebtesam Islam, MD, PhD, Zachary Mulkey, MD and Kenneth Nugent, MD

Abstract: A case of anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis with an atypical finding of transient increased intracranial pressure is reported. Anti-NMDAR encephalitis is an underrecognized, novel and treatable form of encephalitis being increasingly identified as an explanation of encephalitis in young adults. Management of these patients requires a multidisciplinary approach involving neurologists, internists, nursing and rehabilitation staff. It is important for internists to recognize this condition and consider it in the differential diagnosis of encephalopathy. Internists also need to be familiar with the clinical manifestations and the treatment of the disease as they have an important role in the care of these patients during their prolonged stay in the hospital. Increased intracranial pressure is an atypical and underrecognized finding that has been only noted in a previous review on this disorder. It may present a diagnostic or management challenge in patients with anti-NMDAR encephalitis.

Key Indexing Terms: Anti-*N*-methyl-D-aspartate receptor antibodies; Encephalitis; Increased intracranial pressure; Immunotherapy. **[Am J Med Sci 2013;345(6):491–493.]**

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a neuroautoimmune syndrome characterized by psychiatric symptoms, seizures, dyskinesias, autonomic instability and central hypoventilation.[1] The pathogenesis of this disease involves antibody formation systemically and in the central nervous system against NR1 heteromers of NMDAR.[1,2] Because it is a condition that is treatable with fairly good prognosis, internists need to consider the diagnosis in the differential diagnosis of encephalopathy. Understanding the pathophysiology, clinical manifestations and treatment of anti-NMDAR encephalitis is important because internists have a central role in the management of these patients during their prolonged hospital stay. In this article, we present a case of anti-NMDAR encephalitis and review the literature regarding anti-NMDAR encephalitis. Our patient presented with transient increased intracranial pressure, an atypical and underrecognized finding that has been only noted in a previous review on this disorder.[3] This initially presented both a diagnostic and management challenge.

CASE PRESENTATION

A healthy 18-year-old man initially presented to an outside facility with generalized tonic-clonic seizures after a 1-week history of a new onset headache without fever. On initial presentation, the patient was found to be afebrile with normal vital signs. He had an unremarkable general examination, normal routine blood workup and negative urine drug screen results. Head computed tomography and magnetic resonance imaging (MRI) showed no significant acute pathology. Electroencephalography (EEG) did not reveal seizure activity. Cerebrospinal fluid (CSF) from a lumbar puncture showed a white blood cell count of 176 cells per milliliter (66% lymphocytes, 28% neutrophils), a red blood cell count of 34 cells per milliliter, glucose of 54 mg/dL and protein of 53.9 mg/dL. He was treated empirically for bacterial meningitis and Herpes simplex virus (HSV) encephalitis with vancomycin, ceftriaxone and acyclovir for 10 days. A subsequent lumbar puncture 7 days later showed a similar lymphocytic predominant profile. HSV polymerase chain reaction, CSF bacterial antigen panel, and culture test results were negative. He had no repeat episodes of seizure and was discharged home with the diagnosis of seizures due to viral meningitis.

The patient was readmitted to the outside facility 4 days later because of persistent headache, nausea, vomiting and decreased appetite. He was alert and oriented initially. It was thought that his symptoms were due to postlumbar puncture headache, and he was treated with intravenous hydration, an epidural blood patch and sumatriptan with no significant clinical improvement. During the course of this admission, he became progressively unresponsive. He developed an episode of generalized tonic-clonic seizures and was transferred to our hospital for additional care.

On presentation, the patient was found to have repetitive choreoathethotic movements of both upper extremities and orofacial dyskinesias. The patient was obtunded with a Glasgow Coma Scale of 8 (E2V2M4). Neurological examination demonstrated normal muscle tone, and his reflexes were 2+ bilaterally. An EEG showed continuous generalized slow waves with no epileptiform activity; his MRI was unremarkable. A lumbar puncture showed opening pressures of 550 mm H_2O, a white blood cell count of 82 cells per milliliter (96% lymphocytes), a red blood cell count of 8 cells per milliliter, protein of 39 mg/dL and glucose of 69 mg/dL. His CSF also showed 5 oligoclonal bands not present in the serum, the IgG index was 3.77 and IgG synthesis rate was 63.9 mg/24 hours. The elevated opening pressure on the lumbar puncture in our patient was not expected because he was relaxed during the procedure. Fundoscopy showed normal optic discs with no papilledema. A repeat MRI with magnetic resonance venography did not find cerebral venous thrombosis, and there were no signs of brain edema. His MRI showed normal ventricular size. The patient was monitored closely in consultation with neurosurgery with no clinical deterioration. A lumbar puncture performed 2 days later showed a normal opening pressure of 185 mm H_2O. He was not taking antibiotics or vitamin A supplements at the time of both lumbar punctures. The test results of the fungal culture and cryptococcal antigen from the CSF were negative.

During admission, our patient continued to have dyskinetic movements. Autonomic instability characterized by sinus tachycardia and elevated blood pressures was observed. Our patient also demonstrated central hypoventilation and hypersalivation. He was intubated with subsequent tracheostomy performed due to his inability to protect his airway. An extensive

From the Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas.

Submitted September 13, 2012; accepted in revised form September 25, 2012.

There are no conflicts of interest to disclose.

Correspondence: Sian Y. Lim, MD, Department of Internal Medicine, Texas Tech University Health Sciences Center, 3601 4th Street, Lubbock, TX 79430 (E-mail: yik.lim@ttuhsc.edu).

workup for autoimmunity (including antinuclear, antineutrophil cytoplasmic and thyroid peroxidase antibodies), uncommon infections (including CSF polymerase chain reaction for HSV, Cytomegalovirus and Epstein Barr virus, CSF antibodies for Varicella zoster virus, serology for West Nile virus, Eastern Equine encephalitis, Western Equine encephalitis, *Borrelia burgdorferi* and human immunodeficiency virus) and for metabolic disorders (including ammonia, lactate levels) gave negative results. The patient was treated with doxycycline (7 days), acyclovir (14 days) and methylprednisolone (7 days) without any significant change in his mental status. He was also given fosphenytoin for seizure prophylaxis. An assay for NMDAR antibodies in the CSF was eventually reported to be positive and supported the diagnosis of anti-NMDAR encephalitis. In our patient, the workup for malignancy, which included a computed tomography of the chest, abdomen and pelvis, was unremarkable. Ultrasound of the scrotum showed no significant masses, and evaluation of tumor markers for testicular cancer, including α-fetoprotein, β-human chorionic gonadotropin and lactate dehydrogenase, gave negative results.

Our patient was treated with 5 days of intravenous immunoglobulin, high-dose corticosteroids and finally 5 days of plasmapheresis. After plasmapheresis was performed, he was more oriented, was able to follow commands, had decreased dyskinetic movements and was able to stand with assistance after physical rehabilitation. He was transferred to a neurological rehabilitation facility for continued neurorehabilitation and a slow reduction in his corticosteroid dose.

DISCUSSION

Anti-NMDAR encephalitis is being increasingly recognized as a cause of encephalopathy in young adults. It is a neuroautoimmune syndrome. Dalmau et al[1,2] demonstrated that the underlying pathogenesis involves antibody formation systemically and in the central nervous system against the NR1 heteromers of NMDAR. These antibodies cause internalization and capping of NMDAR, which results in a selective decrease in NMDAR surface density, synaptic localization and function. It has been postulated that the clinical manifestations are explained by disinhibition of excitatory pathways and increased extracellular glutamate due to the inactivation of gabanergic neurons that are NMDAR rich.[3]

Anti-NMDAR encephalitis was initially reported as a paraneoplastic limbic encephalitis. Forty-nine percent of women with anti-NMDAR encephalitis have tumors (>90% were ovarian teratomas).[3] Therefore, young women with anti-NMDAR encephalitis should be screened for ovarian teratomas. Ovarian teratomas associated with anti-NMDAR encephalitis express NMDAR, and this may represent the immunological trigger for the development of NMDAR antibodies.[4] In contrast, only 5% of men had an underlying tumor.[3] In cases with no evidence of malignancy, the immunological trigger for the development of NMDAR antibodies remains unclear.

Symptoms in anti-NMDAR encephalitis present as a sequential multistage process. The prodromal phase is characterized by nonspecific symptoms, such as fever, malaise, headache, nausea and vomiting. This is followed by a psychotic/seizure phase in which behavioral disturbances (including psychosis, depression, apathy and fear) and generalized tonic-clonic/complex seizures occur. Patients then become unresponsive and develop autonomic instability, dyskinesias, extrapyramidal signs and stereotyped motor automatisms.[3] Transient increased intracranial pressure is an atypical and underrecognized finding that has been only noted in a previous review on this disorder.[3] The increased intracranial pressure in our case was transient and benign. Close monitoring and consultation with neurosurgery is warranted in managing cases with increased intracranial pressure. The mechanism of the transient increase in intracranial pressure in our case is unclear in view of normal MRI findings. This could be possibly related to the dysregulation of glutaminergic transmission leading to vasodilation of cerebral blood vessels.

The diagnosis of anti-NMDA receptor encephalitis is based on clinical presentation and the detection of NMDAR antibodies in the serum and CSF. NMDAR antibodies are usually detected in both serum and CSF, but in some cases, only the CSF is positive for NMDAR antibodies.[3] Intrathecal synthesis of NMDAR antibodies is seen in most patients. In the CSF, lymphocytic pleocytosis, mild elevations of protein and CSF-specific oligoclonal bands are also found. Toxic, metabolic, viral, autoimmune and psychiatric etiologies should be considered in the differential diagnosis (Table 1). Fifty percent of patients have normal findings on MRI. Reported anomalies on MRI include nonspecific hyperintensities on T2 or fluid-attenuated inversion recovery scans in various areas of the brain. EEGs typically show nonspecific generalized slow activity.

Definitive treatment of anti-NMDAR encephalitis involves immunotherapy, and detection and treatment of any tumors, especially ovarian teratoma. The first-line immunotherapy in anti-NMDAR encephalitis includes plasmapheresis, intravenous immunoglobulins, and/or methylprednisolone. Early detection and treatment of teratomas with the initiation of immunotherapy has been associated with better outcomes.[1] Cases without teratomas are more likely to require second-line immunotherapy, which includes cyclophosphamide, rituximab or both.[3] The prognosis of anti-NMDAR encephalitis is fairly good, and almost 75% of patients recover with only mild neurological deficits.[3]

The recognition of autonomic manifestations that include tachycardia, bradycardia, hypo/hyperthermia, labile blood

TABLE 1. Differential diagnosis of anti-NMDAR encephalitis

Viral encephalitides
Herpes simplex virus
Enterovirus
Rabies
Arbovirus
Autoimmune encephalitides
Anti-LGI1 encephalitis
Anti-AMPA receptor encephalitis
Paraneoplastic limbic encephalitides-anti-Hu, anti-Ma2
Systemic lupus erythematosus cerebritis
Antiphospholipid syndrome
Hashimoto's encephalopathy
Psychiatric disorders
Psychosis
Schizophreniform disorder
Neuroleptic malignant syndrome
Serotonin syndrome
Toxic and metabolic disorders
Toxic ingestion
Porphyria
Mitochondrial disorders
Disorders of amino or organic acid metabolism

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LGI1, leucine-rich glioma inactivated 1.

pressure and hypersalivation is important in managing patients with anti-NMDAR encephalitis. A high index of suspicion for hospital-acquired conditions such as thromboembolic events and nosocomial infections is needed. Adequate workup should be pursued before attributing any abnormal physiological findings to autonomic instability. If the workup results are negative, treatment of abnormal vital sign parameters should be instituted only when there is severe physiological compromise. Antimicrobial agents should be used only when there is a clear source of infection. Sixty-six percent of patients with anti-NMDAR encephalitis may develop central hypoventilation[1] and require intubation and mechanical ventilator support. Generalized tonic-clonic seizures, complex partial seizures, and status epilepticus in anti-NMDAR encephalitis need to be differentiated from choreoathethotic movements and dystonia to avoid undertreating seizures or unnecessary escalation of antiepileptics. Monitoring with video EEG has been recommended.[4]

CONCLUSIONS

In summary, a case of anti-NMDAR encephalitis is presented. It is important for internists to consider anti-NMDAR encephalitis in the differential diagnosis of encephalopathy. Although this disease needs more investigation, understanding the pathophysiology, clinical manifestations and treatment of anti-NMDAR encephalitis will be important for the internists who will be managing this novel encephalitis in conjunction with other subspecialists and ancillary staff.

REFERENCES

1. **Dalmau J, Gleichman AJ, Hughes EG, et al.** Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
2. **Dalmau J, Tuzun E, Wu HY, et al.** Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
3. **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.
4. **Florance NR, Davis RL, Lam C, et al.** Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11–8.