Case Report/Case Series

Herpes Simplex Encephalitis as a Potential Cause of Anti–*N*-Methyl-D-Aspartate Receptor Antibody Encephalitis
Report of 2 Cases

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IMPORTANCE Encephalitis mediated by anti–*N*-methyl-D-aspartate (NMDA) receptor antibodies and herpes simplex (HS) encephalitis are seemingly separate causes of encephalopathy in adults and children. Herpes simplex encephalitis is infectious, and anti-NMDA receptor antibody encephalitis is autoimmune in origin. Both can cause seizures and encephalopathy, although the latter can also cause psychiatric symptoms and movement disorders. Owing to the rarity of these 2 diseases, patients with co-occurrence are important because they alert clinicians to possible links between 2 seemingly separate processes.

OBSERVATIONS In a case series of 2 patients observed at our center, we describe an infant and an adult who had confirmed HS encephalitis and then developed confirmed anti-NMDA receptor antibody encephalitis. Polymerase chain reaction testing for HS virus was performed. Testing for NMDA receptor antibodies was performed by Associated Regional and University Pathologists Laboratory in Salt Lake City, Utah.

CONCLUSIONS AND RELEVANCE We conclude that atypical cases of HS or other viral encephalitides should be investigated for concomitance of an autoimmune encephalitis. We suspect that the pathophysiologic mechanisms by which HS virus infects neurons produce a higher likelihood of contracting anti-NMDA receptor antibody encephalitis.

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Anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies are an increasingly recognized cause of encephalitis. Patients can present with encephalopathy, subacute behavioral changes, seizures, and occasionally a movement disorder.[1-4] Anti-NMDA receptor antibody encephalitis often occurs without clear provocation. Although tumors have been seen in approximately 50% of adult patients, they are much less common in pediatric patients.[3,5]

Recently, anti-NMDA receptor IgG antibodies have been detected in up to 11% of a small series of patients with herpes simplex (HS) encephalitis,[6] and these authors also demonstrated IgA and IgM reactivity in their series. In that report, patients with previous HS encephalitis diagnosed by polymerase chain reaction (PCR) findings of HS virus (HSV) DNA in the cerebrospinal fluid (CSF) were found to have anti-NMDA receptor antibodies. In our report, we present an additional 2 cases with confirmed HS encephalitis who subsequently developed anti-NMDA receptor antibody encephalitis. Furthermore, an additional case series by Armangue et al[4] described a similar presentation in a 2-year-old girl. These time courses suggest a possible link between HSV-mediated neuronal damage and subsequent anti-NMDA receptor antibody–mediated disease, a theory also proposed by Prüss and colleagues.[6] If true, this theory might represent a need to shift treatment options for patients with encephalitis.

Report of Cases

Case 1

A male infant presented with deteriorating mental status and persistent twitchy movements for several months. When the patient was born, he had an eye infection that was confirmed to be HSV of unspecified type by culture findings and PCR analysis, according to reports from a nonaffiliated hospital. He was treated with 21 days of intravenous acyclovir sodium followed by 6 months of oral acyclovir. He progressed well, with normal development. About 3 months before his diagnosis, he was noted to have hyperkinetic movements in his feet that were thought to be normal infant movements by his family. One day before admission, he had a seizure; after a lumbar puncture at admission, he was noted to have HSV-2 in his CSF sample, as confirmed by PCR findings. For his initial lumbar puncture, his CSF white blood cell (WBC) count was 94/μL; red blood cell (RBC) count, 1.4 ×10^6/μL; and differential count, 72% lymphocytes, 14% polymorphonuclear cells, 12% monocytes/

macrophages, and 2% eosinophils. His initial CSF protein level was 34 mg/dL and CSF glucose level was 48 mg/dL. (To convert WBC count to $\times 10^9$ per liter, multiply by 0.001; RBC count to $\times 10^9$ per liter, by 1; differential counts to proportions of 1, multiply by 0.01; and glucose level to millimoles per liter, multiply by 0.0555.) Magnetic resonance imaging also revealed an extensive right temporal lobe lesion.

Intravenous acyclovir therapy was initiated, but progressive neurological deterioration continued. Although he had been babbling and even started to say words, he became nonverbal. His attention to his mother worsened, and he had longer and longer periods of nonresponsiveness, although he appeared awake. In addition, the twitchy movements in his legs extended to involve his upper extremities, and he developed orofacial dyskinesias. Examination revealed a child with poor head control, a right gaze preference, and nearly continuous diffuse choreoathetosis. He underwent a second lumbar puncture after more than 21 days of intravenous acyclovir therapy, with PCR findings negative for HSV. For this second lumbar puncture, his CSF WBC count was 77/μL; RBC count, 2.2 $\times 10^6$/μL; and differential count, 87% lymphocytes, 10% monocytes/macrophages, 2% eosinophils, and 1% basophils. A third lumbar puncture performed 1 week later was positive for anti-NMDA receptor antibodies. A titer of 1:10 was sent to Associated Regional and University Pathologists Laboratory in Salt Lake City, Utah; PCR results for HSV in this specimen were also negative. Previous samples had not been analyzed for anti-NMDA receptor antibodies because his presentation was consistent with HSV central nervous system infection. In addition, his CSF WBC count for that lumbar puncture specimen was 62/μL; RBC count, 0.2 $\times 10^6$/μL; and differential count, 76% lymphocytes, 20% monocytes/macrophages, 3% eosinophils, and 1% basophils. A protein level of 52 mg/dL and a glucose level of 44 mg/dL were found in the CSF.

While awaiting test results, he was treated with intravenous immunoglobulin, 2 g/kg, divided among 5 days. Because we noted no improvement with intravenous immunoglobulin therapy, plasma exchange was initiated. By this time, his test results had confirmed the diagnosis of anti-NMDA receptor antibody encephalitis. Screening with an ultrasonographic examination of his testicles and a computed tomographic scan of his chest, abdomen, and pelvis showed no evidence of tumors. Also, serum test results were negative for Purkinje cell antibodies and neuronal nuclear antibodies. After 7 plasma exchange sessions, we noted only minimal improvement in the immediate follow-up period.

After his discharge from the hospital, his mother reported that he gradually became increasingly responsive during a period of 2 weeks. Three weeks after the completion of his last plasma exchange, he was saying "dada," smiling, cooing, and starting to regain his motor milestones. Follow-up is ongoing.

Case 2

A previously healthy white man in his 20s presented to a hospital with frequent headaches, malaise, and 1 week of confusion. He was found obtunded at home and brought to a local emergency department, where he was found to be febrile. Magnetic resonance imaging revealed bitemporal edematous lesions, greater on the left than the right sides. He underwent a lumbar puncture. Results of CSF analysis were notable for a WBC count of 128/μL with 87% lymphocytes, an RBC count of 0.1 $\times 10^6$/μL, and a protein level of 130 mg/dL. Results of the PCR analysis were positive for HSV, and he was treated with 21 days of intravenous acyclovir sodium at a dose of 8 to 10 mg/kg 3 times a day. No testing for anti-NMDA receptor antibodies was performed at that time. He improved clinically and was discharged to home being able to speak with some expressive aphasia and with clear cognitive deficits. Within 1 week at home, his speech declined and he began having behavioral changes. He was readmitted, and a second CSF analysis was performed to ensure clearance of the HSV infection. Results of PCR analysis were negative for HSV, but a CSF protein level of 239 mg/dL and WBC count of 25/μL (81% lymphocytes) were found. He was treated for possible seizures and with antipsychotics for behavior control and released to a rehabilitation facility. Shortly after his release, a serum anti-NMDA receptor antibody test sent to Associated Regional and University Pathologists Laboratory was positive, without titer measurement. He was readmitted to a facility, and a third CSF analysis showed a WBC count of 4/μL, a protein level of 182 mg/dL, and negative findings for HSV DNA by PCR. He continued acyclovir therapy for 1 week while awaiting confirmation of anti-NMDA receptor antibody results but also initiated plasma exchange therapy. During these exchanges, his speech improved and he was able to follow some commands. He was subsequently treated with a course of intravenous immunoglobulin, 2 g/kg divided among 5 days. He achieved some additional improvement and was transitioned to rehabilitation. He continued to have some deficits despite rehabilitation and received cyclophosphamide, 1 g/m^2. This dosage was repeated monthly, and the patient made some modest improvements. He was ambulatory and verbal and could process simple tasks. He had ongoing episodic outbursts. Magnetic resonance imaging revealed chronic bifrontal and temporal damage consistent with his prior HSV infection.

Discussion

These 2 cases illustrate an observed association between HS and anti-NMDA receptor antibody encephalitis. Although this association has been noted in 2 prior publications,[4,6] our observations suggest that such an association may be more common than previously thought. In one of the previously noted series of patients with NMDA receptor antibody encephalitis,[4,7,8] residual choreoathetotic movements after HSV infection were believed to be particularly associated with an autoimmune disorder or anti-NMDA receptor antibody encephalitis. Whether a particular facet of HSV infection triggers this autoimmune encephalitis remains unclear, but we would strongly recommend testing for anti-NMDA receptor antibodies in patients who have persistent

encephalopathy, regression after initial improvement, or persistent movement disorders. Neuronal infections, such as with HSV, may trigger subsequent anti-NMDA receptor antibody formation. Clinicians should consider concomitant treatment or testing for immune-mediated encephalitis when treating viral encephalitis, especially in atypical cases.

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