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 diseases, patients with co-occurrence are important because they alert clinicians to possible links between 2 seemingly separate processes.

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.

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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For this second lumbar puncture, his CSF WBC count was no acyclovir therapy, with PCR findings negative for HSV. Second lumbar puncture after more than 21 days of 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 277/μL; RBC count, 2.2 ×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 ×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 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 ×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 anti-psychotics 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/m². 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, 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, 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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REFERENCES