Case of concurrent herpes simplex and autoimmune encephalitis

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An association between herpes simplex virus (HSV) encephalitis and NMDA receptor (NMDAR) encephalitis has been well described. Here, we report a rare case of HSV encephalitis occurring alongside autoimmune encephalitis with leucine-rich glioma inactivated 1 (LGI-1) and NMDAR antibodies.

Case report

An 84-year-old woman presented to the hospital with 3 days of progressive dizziness, fevers, and confusion. Serum sodium was 123. MRI of the brain showed T2 fluid-attenuated inversion recovery (FLAIR) hyperintensity of the medial right temporal lobe and right insular cortex with patchy diffusion restriction (figure). IV acyclovir was initiated, and lumbar puncture was performed one day later, showing 7 red blood cells, 0 nucleated cells, elevated protein (91), normal glucose (42), and positive HSV PCR in the CSF. Treatment with IV acyclovir led to initial clinical improvement, and she was discharged to a rehabilitation facility. After 1 week, she deteriorated with worsening confusion. Serum LGI-1 antibody via cell-based assay returned positive, titer of 1:20, whereas the remainder of the autoimmune antibody panel was negative, including NMDAR antibodies (Quest Diagnostics). She was treated with 5 days of IV immunoglobulin. Her mental status continued to decline, and she was transferred to our tertiary care center 3 weeks after her initial presentation.

On examination, she had poor attention and followed only simple commands. She had intermittent episodes of brief left facial grimacing with contraction of the left arm consistent with faciobrachial dystonic seizures. These had not occurred before her hospitalization. Continuous EEG monitoring showed intermittent nonconvulsive seizures arising from the left temporal lobe independent of her abnormal movements. These were eventually controlled with levetiracetam, valproic acid, and lacosamide. Serum sodium remained low (130). MRI of the brain was repeated and showed worsening right temporal lobe T2 FLAIR hyperintensity and hemorrhage into the right medial temporal lobe. Repeat lumbar puncture after 21 days of acyclovir demonstrated 8 red blood cells, 76 nucleated cells (99% lymphocytes), elevated protein (89), and normal glucose (52). CSF HSV PCR was repeated and was negative. Anti-LGI-1 antibodies were positive by cell-based assay in the CSF and serum. CSF NMDAR antibody was also positive by undiluted cell-based assay and was negative at 1:2 dilution by tissue-based assay. Serum NMDAR antibody by cell-based assay was negative (Mayo Clinic Laboratories). She was treated with a 5-day course of IV methylprednisolone and continued on IV acyclovir. Her level of arousal improved for 2 weeks but then plateaued, at which point she was given rituximab. Over the ensuing 2 weeks, her mental status began slowly improving and she was discharged to a rehabilitation center. However, she developed recurrent episodes of aspiration pneumonia because of persistent dysphagia and was transitioned to hospice care 4 months after discharge.

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Figure MRI of the brain at time of initial presentation

Axial slices of MRI of the brain performed on initial presentation shows diffusion restriction (panels A-C) and T2 FLAIR hyperintensity (panels D-F) of right temporal lobe and right insular cortex. There was no abnormal enhancement on postgadolinium sequences (not shown). FLAIR = fluid-attenuated inversion recovery.

Discussion

There is a well-documented association between HSV and autoimmune encephalitis, specifically NMDAR encephalitis.¹ There are 2 proposed mechanisms for the association between viral and autoimmune encephalitis. A viral-induced inflammatory response in the limbic system may lead to release of NMDAR epitopes, allowing an autoimmune response to ensue. It is also possible that viral proteins trigger an immune response against a similar epitope in the NMDAR, a form of molecular mimicry.² In one prospective analysis, it was demonstrated that among patients who developed autoimmune encephalitis after HSV infection, 36% had antibodies to neuronal antigens other than NMDAR.¹ Taken together with our case, this suggests that similar to the NMDAR, other neuronal epitopes such as LGI-1 can be uncovered by local inflammation and promote an autoimmune response.

The patient's positive CSF HSV PCR, for which the sensitivity and specificity are >94%, argues that HSV infection was truly present.³ Moreover, her MRI of the brain showed a hemorrhagic encephalitis, which is common with HSV encephalitis but is rare with autoimmune limbic encephalitis. The decision to treat with immunosuppression despite evidence of HSV infection was not made lightly. The patient had clinically responded to the initial course of acyclovir, and her subsequent deterioration was likely because of undertreated autoimmune encephalitis, suggesting that more aggressive management was needed. Although she had certain signs of typical LGI-1 encephalitis, such as faciobrachial dystonic seizures, limbic encephalitis, and hyponatremia, her poor responsiveness to immunotherapy was atypical. She was maintained on an extended course of acyclovir throughout her course of methylprednisolone and rituximab initiation to limit the risks of infection reactivation.

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Name	Location	Contribution
John Peters, MD	Department of Neurology, Yale University School of Medicine	Acquisition and review of clinical data, literature search, manuscript preparation, and review
Sarah Wesley, MD, MPH	Department of Neurology, Yale University School of Medicine	Acquisition and review of clinical data, manuscript preparation, and review

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