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HERPES SIMPLEX VIRUS 1 ENCEPHALITIS ASSOCIATED WITH VOLTAGE-GATED CALCIUM CHANNEL AUTOIMMUNITY

Encephalitis is a significant cause of morbidity and mortality, yet a causative factor is identified in <50% of cases.¹ The most common causes are infectious (particularly herpes simplex virus [HSV]) and autoimmune.² Diagnosis of the latter potentially treatable cause is aided by the detection in serum or CSF of an informative profile of autoantibodies against neuronal intracellular proteins and plasma membrane proteins (e.g., voltage-gated potassium channel [VGKC] complex and calcium channels [VGCC, P/Q-type or N-type] and a growing list of glutamate receptors [R] and other autoantibodies of synaptic specificity).^{3,4} Neural autoantibodies, particularly NMDA-R-IgG, have recently been reported in the setting of viral encephalitis.^{5,6} Herein, we report a unique case of N-type VGCC autoantibody temporally associated with HSV encephalitis.

Case report. Five days after an upper respiratory tract infection treated with azithromycin, a 33-year-old woman presented with a tonic-clonic seizure associated with a several-day progressive illness consisting of fever, headache, meningismus, word-finding difficulty, and confusion. The only abnormalities on examination were nuchal rigidity, severe recall deficiency, mild anomia, and semantic paraphasic errors without other language difficulties.

Head and neck CT angiogram was normal. Brain MRI showed restricted diffusion with T2 fluid-attenuated inversion recovery signal hyperintensity and swollen left hypothalamus and medial temporal lobe. EEG demonstrated left temporal periodic discharges. CSF contained 7 nucleated cells/ μ L (90% neutrophils), 295 erythrocytes/ μ L, and normal glucose and protein. Empiric acyclovir treatment was begun for presumed HSV encephalitis (subsequently confirmed by positive CSF HSV-1 PCR).

After initial improvement, right superior temporal quadrantanopsia with right lateral rectus palsy developed on hospital day 8. Brain MRI demonstrated worsened edema (figure). IV dexamethasone was initiated (4 times per day). On hospital day 11, with no clinical response to corticosteroids, positive N-type VGCC autoantibody was reported in the

pretreatment serum (0.12 nmol/L [normal 0.00–0.03 nmol/L]). NMDA, AMPA, GABA_B receptor, and glutamic acid decarboxylase-65 antibodies were negative. Contrasted CT scans of the chest, abdomen, and pelvis were unremarkable.

IV immune globulin (IVIg) was initiated (5 days). After only 1 day, the patient's neurologic status improved significantly. After 5 days, she was discharged to complete a 21-day course of IV acyclovir and to continue oral prednisone (tapering doses) and levetiracetam therapy.

Twelve weeks after discharge, the serum VGCC autoantibody level was lower (0.07 nmol/L). She received IVIg 2 g/kg over 4 days every 12 weeks. Four months after discharge, she remained seizure-free. Her memory and language deficits gradually improved.

Discussion. Detection of N-type VGCC antibody suggested the coexistence of autoimmune encephalitis with HSV encephalitis in this patient. The diagnosis of autoimmune encephalitis was supported by the clinical course and improvement with IVIg accompanied by gradual reduction in the N-type VGCC antibody level. This represents a unique report of autoimmune encephalitis associated with HSV encephalitis. Both HSV DNA and N-type VGCC autoantibody were detected in the pretreatment specimens of CSF and serum, respectively. A causal relationship between the 2 entities cannot be established conclusively. The patient's favorable responses initially to acyclovir and subsequently to IVIg support both viral and autoimmune contributions to the encephalitis, although this does not necessarily indicate that the antibody was pathogenic. The N-type VGCC antibody was proven to be IgG class by immunoprecipitation with IgG isotype-specific secondary antibodies. Detection of IgM class might have been considered evidence of a newly arising immune response. The evolution of autoimmunity in relation to HSV infection remains to be elucidated.² One potential explanation is viral lysis of host neurons leading to an autoimmune response. Alternatively, subclinical perturbation of the neurons by a preexistent neuronal autoantibody could have activated resident latent HSV virus, with subsequent amplification of the autoimmune response by neuronal antigens released through lytic

Figure Brain MRI

Brain MRI on hospital day 8 demonstrated increased edema in the anterior left temporal lobe and hippocampus with mild left uncus herniation and restricted diffusion along the left subinsular cortex and anterior left temporal lobe cortex.

viral infection. Finally, a polyclonal response to infection may have amplified a preexisting asymptomatic neuronal autoantibody.

Autoimmune encephalitides, once considered rare, are increasingly recognized as significant causes of encephalitis. Their clinical presentations and immunologic etiologies vary.⁷ An autoimmune etiology should be considered early in the differential diagnosis of encephalitis, particularly when the patient does not respond to anti-viral therapy or paradoxically deteriorates.

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Author contributions: Michael J. Bradshaw, MD: design, chart review, manuscript preparation. Siddharama Pawate, MD: manuscript editing. Vanda A. Lennon, MD, PhD: manuscript editing, laboratory studies. Karen C. Bloch, MD, MPH: manuscript editing. Kelly M. Brown, MD: manuscript editing.

Study funding: No targeted funding reported.

Disclosure: The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received May 15, 2015. Accepted in final form August 10, 2015.

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CEREBRAL HYPERPERFUSION ON ARTERIAL SPIN LABELING MRI DURING CADASIL MIGRAINOUS ENCEPHALOPATHY

Migrainous encephalopathy is a rare and poorly understood manifestation of the inherited vasculopathy cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Patients may present with migraine with aura, complicated by confusion, fever, and decreased conscious level.¹ In this case, a patient with migrainous encephalopathy underwent cerebral perfusion imaging with arterial spin labeling (ASL) MRI before, during, and following admission.

Case report. A 27-year-old man with CADASIL associated with the NOTCH3 mutation pArg133Cys, diagnosed in 2011, noticed his vision to the right side was like “looking through a hole.” Over the next 30 minutes, complete distortion of vision to the right along with altered sensation and reduced power in his right

arm occurred, followed by a severe pulsating bilateral frontal headache associated with nausea.

After 3 hours, he was admitted to the hospital and was drowsy with symmetrical weakness in all limbs. Speech was slow but there was no dysphasia, eye movement abnormality, or ataxia. Headache was ongoing. Systemic examination was normal. He was afebrile and normotensive. Full blood count, erythrocyte sedimentation rate, C-reactive protein, urea, and electrolytes were normal. CT head showed no evidence of acute intracranial pathology. CSF examination was not performed.

The following morning, the patient had disconjugate and slowed eye movements, profound motor and cognitive slowing, extensor plantars, and global motor weakness. CT angiogram was normal. Diffusion-weighted MRI demonstrated no evidence of acute ischemia. MRI was unchanged from imaging 4 months previously, with subcortical and deep white matter T2