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ZOSTER SINE HERPETE: VIROLOGIC VERIFICATION BY DETECTION OF ANTI-VZV IgG ANTIBODY IN CSF

Classic zoster sine herpete (ZSH) is defined clinically as dermatomal distribution pain without rash. ZSH was designated as a nosologic entity based on virologic confirmation in 3 men over age 60 with chronic thoracic-distribution radicular pain, with amplifiable varicella zoster virus (VZV) DNA found in CSF of the first 2 patients[1] and in blood mononuclear cells (MNCs) in the third patient.[2] Herein, we describe a patient who developed radicular pain without rash in the same dermatome as his initial cervical-distribution zoster episode, but with a remarkably prolonged interval between episodes, and in whom ZSH was virologically confirmed by the detection of anti-VZV immunoglobulin G (IgG) antibody in CSF with serum/CSF ratios indicative of intrathecal antibody synthesis.

Case report. In 2008, a 77-year-old man developed right C8-distribution zoster; he was not treated with an antiviral agent or steroids and his rash and pain resolved completely. One year later, he developed colon cancer and was treated every other week for 7 months with a protocol using leucovorin, 5-fluorouracil, oxaliplatin, and folinic acid.[3] In November 2009, right C7–8-distribution pain recurred, but in the absence of rash. In December 2009, he developed a painless right foot drop. In February 2010, neurologic examination revealed C7–8 thigmesthesia and allodynia and an incidental right peroneal palsy. All deep tendon reflexes were reduced or absent. Cervical MRI revealed degenerative changes at C5–6 and C6–7 without root compression. The CSF was acellular; cytology was negative, and CSF protein was 87 mg%. A presumptive diagnosis of ZSH was made, and he was treated with valacyclovir, 1 g 3 times daily for 14 days, and pregabalin, 150 mg at night. A few days after treatment, he experienced a dramatic reduction in pain, and 2 months later, was pain-free. Virologic studies of the CSF and serum obtained before antiviral treatment revealed no amplifiable VZV or herpes simplex virus (HSV) DNA and no anti-HSV IgG antibody. In contrast, anti-VZV IgG antibody was present, and the serum/CSF ratio of anti-VZV IgG antibody was markedly reduced (4.9) compared to ratios for albumin (70) and total IgG (150), indicative of intrathecal synthesis of anti-VZV IgG.

Discussion. Analysis of our patient revealed 2 remarkable features. First, although the development of radicular pain without rash in the same dermatome as earlier zoster in our patient is much like the earlier description of radicular pain without rash days after zoster in a different dermatome,[4] the prolonged interval of 18 months from zoster to later-onset ZSH is unique. Second, intrathecal synthesis of anti-VZV IgG antibody in CSF provided virologic proof of zoster sine herpete; in fact, unlike the other 3 patients with ZSH in whom PCR revealed VZV DNA in CSF[1] or blood MNCs,[2] our patient's CSF was negative for VZV DNA.

Importantly, intrathecal synthesis of anti-VZV IgG antibody has been shown to be a superior parameter as compared to detection of VZV DNA in CSF in diagnosing VZV vasculopathy,[5] and VZV myelopathy in the absence of rash in patients whose CSF did not contain VZV DNA.[6,7] Nevertheless, the comparative diagnostic value of these tests awaits virologic analysis in additional cases of ZSH. Until then, CSF should be examined for both VZV DNA and anti-VZV IgG antibody in patients with prolonged radicular pain without rash to verify the diagnosis of zoster sine herpete.

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GERSTMANN-STRÄUSSLER-SCHEINKER DISEASE DUE TO A NOVEL PRION PROTEIN GENE MUTATION

Prion diseases are rapidly progressive, fatal brain disorders arising sporadically, genetically, or by infection.[1] Dominant, high-penetrance mutations in the gene (*PRNP*) encoding the prion protein (PrP) cause 5%–15% of human cases.[2] Gerstmann-Sträussler-Scheinker (GSS) disease is an exceedingly rare inherited phenotype,[2] defined neuropathologically by multicentric, PrP-containing amyloid plaques. We present a patient with prominent seizures, cognitive decline, and ataxia who was found to have a novel mutation in *PRNP*.

Case report. A 34-year-old man presented in status epilepticus. Despite multiple anticonvulsants, he continued to have complex partial and generalized tonic-clonic seizures. He developed an unsteady gait, slurred speech, and personality change marked by disinhibition. Three years prior, he had onset of gradual cognitive decline, which accelerated following the onset of epilepsy. Eight years prior, the patient had developed night terrors, which resolved spontaneously after 6 years. Otherwise, the patient was healthy. His 7-year-old son was recently diagnosed with Asperger syndrome.

Examination showed a Montreal Cognitive Assessment score of 15/30. Neuropsychiatric assessment revealed memory and executive function deficits. The patient demonstrated saccadic pursuit, square wave jerks, and flaccid dysarthria. Power and reflexes were normal; plantar responses were flexor. There was diffuse paratonia and axial rigidity. Finger-to-nose testing was normal but he had mild difficulty with heel-to-shin testing. Rapid alternating movements were impaired by apraxia. Gait was slightly wide-based. Nonstimulus-sensitive myoclonus was present.

The patient underwent extensive investigations (table e-1 on the *Neurology*® Web site at www.neurology.org). Brain MRI on multiple occasions showed mild diffuse cortical atrophy and mild cerebellar vermian atrophy without restricted diffusion or gadolinium enhancement (figure 1, A–C). Video-EEG demonstrated diffuse slowing consistent with an encephalopathy and high-amplitude multifocal epileptiform discharges with accentuation bifrontally and over the left posterior temporal region (figure e-1). Pathologic examination of a right middle frontal gyrus biopsy (figure 1, D–G) revealed mild neuronal loss, microspongiosis, and multicentric plaques consistent with GSS. CSF drawn 5 days after the brain biopsy was positive for 14–3-3 protein by immunoblot (SC-1657 primary antibody; cutoff ≅1.5 ng recombinant γ 14–3-3 protein per lane) and positive (1,378 pg/mL) for total tau protein (Innogenetics hTAU® ELISA; cutoff 1,300 pg/mL).[3]

PRNP was sequenced from lymphocyte-derived genomic DNA. The patient was heterozygous for a novel allele with a 24-nucleotide insertion encoding an 8–amino acid insertion (figure 1, H). The normal allele lacking the insertion carried a Val codon (GTG) at polymorphic codon 129 (figure 1, H). The patient's parents both lacked the novel insertion allele.

Discussion. We identified a novel *PRNP* allele (365–388 dup), almost certainly causing GSS, in a young patient with slowly progressive dementia. Two types of mutations in the *PRNP* gene have been previously recognized: point mutations and alter-

Supplemental data at www.neurology.org