James Wolf, MD
Maria A. Nagel, MD
Ravi Mahalingam, PhD
Randall J. Cohrs, PhD
D. Scott Schmid, PhD
Don Gilden, MD

CHRONIC ACTIVE VARICELLA ZOSTER VIRUS INFECTION

This case report illustrates previously undescribed features of chronic active varicella zoster virus (VZV) infection, including a 4-month delay between the onset of zoster and zoster sine herpete, involvement of 9 dermatomes on progression of zoster to zoster sine herpete, and the presence of both VZV DNA and anti-VZV immunoglobulin G (IgG) in the CSF.

Case report. In July 2010, a 58-year-old insulin-dependent diabetic woman developed right-sided T3–4 distribution zoster treated with valacyclovir, 1 g TID for 10 days. Pain persisted. Two months later, she was retreated for 10 days without pain relief. In November 2010, she experienced left-sided T5–8 radicular pain. Neurologic examination revealed left-sided T5–10 hypalgesia. Pain continued. In February 2011, thoracic MRI was normal. She declined electrodiagnostic studies. In April 2011, persistent left T5–8 pain expanded rostral to T2 and caudal to T10. CSF was acellular; protein 123 mg%; no oligoclonal bands. Virologic analysis revealed 5,600 copies of VZV DNA per mL of CSF, but not herpes simplex virus (HSV) DNA or anti-HSV antibody. Anti-VZV IgG antibody was found in CSF, and serum/CSF ratio of anti-VZV IgG antibody was markedly reduced (7.6) compared to ratios for albumin (56) and total IgG (92), indicating intrathecal synthesis of anti-VZV IgG. No VZV DNA was found in blood mononuclear cells or saliva on 4 consecutive days. In May 2011, she was treated with IV acyclovir, 10 mg/kg TID for 3 weeks. Three weeks later, pain decreased "70%–80%." She was maintained on oral valacyclovir, 1 g TID for 6 more weeks, and continued to improve. In July 2011, because of financial problems, she stopped insulin; 1 month later, blood glucose level was 283 mg% and left-sided pain "increased 50%." Her diabetes was then treated with metformin and she was restarted on antiviral therapy, with considerable improvement in pain.

Discussion. Our patient developed classic right-sided T3–4 distribution zoster complicated by postherpetic neuralgia (PHN). Four months after zoster, she developed left-sided pain without rash involving 4 dermatomes (T5–8). Within another 5 months, the left-sided pain spread rostrally to T2 and caudally to T10, indicating involvement of 9 dermatomes. At this time (9 months after zoster), VZV DNA and anti-VZV IgG antibody were found in CSF. Overall, when our patient experienced PHN on the right and extensive zoster sine herpete on the left, virologic analysis revealed active VZV infection.

This unique case illustrates multiple heretofore undescribed and remarkable features of chronic active VZV radiculopathy. First, the interval between zoster and zoster sine herpete is usually only days,[1] in contrast to the development of zoster sine herpete in our patient 3 months after zoster. Second, zoster followed by zoster sine herpete does not progress to involve 9 dermatomes as in our patient. Third, while original cases of zoster sine herpete were verified virologically by detection of VZV DNA[2] or anti-VZV IgG antibody in CSF,[3] our patient had both abundant VZV DNA and anti-VZV IgG antibody in CSF.

It is possible that chronic VZV radiculopathy, multidermatomal pain, and its persistence after oral antiviral treatment were due in part to diabetes, which increases the risk for VZV reactivation. Compared to the well-known decline in VZV-specific cell-mediated immunity (CMI) in healthy individuals with increasing age, diabetic patients stratified by decade have even lower CMI responses to VZV[4] and are at significantly higher risk for zoster.[5]

Protracted zoster sine herpete in multiple dermatomes distinct from the site of the patient's initial zoster indicates chronic active VZV ganglionitis. Chronic VZV ganglionitis also presents as 1) prolonged pain without rash in individuals with no history of zoster[2]; 2) prolonged pain (preherpetic neuralgia) before zoster rash; and 3) longstanding radicular pain due to an inflammatory ganglionic mass productively infected with VZV.[6] The ability of VZV to reactivate from some dermatomes with rash and from other dermatomes without rash is supported by studies with simian varicella virus (SVV), the counterpart of human VZV, in monkeys, where productive SVV virus infection was found in ganglia

on the opposite side of the neuraxis 1–4 months after zoster.[7]

Finally, clinical-virologic correlation in our patient, along with resolution of both right-sided PHN and left-sided zoster sine herpete after IV antiviral treatment, strongly suggests that PHN is due to chronic active VZV ganglionitis. Although neither PHN nor zoster sine herpete has been treated effectively with oral antiviral therapy, zoster sine herpete resolved after treatment with IV acyclovir.[2] If active VZV infection is diagnosed in patients with PHN, IV treatment with acyclovir may be helpful, as it was in our patient.

From the Department of Neurology (J.W.), Greater Baltimore Medical Center, Baltimore, MD; the Departments of Neurology (M.A.N., R.M., R.J.C., D.G.) and Microbiology (D.G.), University of Colorado School of Medicine, Aurora; and National Center for Infectious Diseases (D.S.S.), Centers for Disease Control and Prevention, Atlanta, GA.

Author contributions: All authors had full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors contributed to the study concept and design; data acquisition; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and study supervision.

Acknowledgment: The authors thank Marina Hoffman for editorial assistance.

Study funding: Supported in part by NIH grants AG006127 and NS32623 to D.G. and NS067070 to M.A.N.

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

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Received February 9, 2012. Accepted in final form March 21, 2012.

Correspondence & reprint requests to Dr. Gilden: Don.Gilden@ucdenver.edu

1. Lewis GW. Zoster sine herpete. BMJ 1958;2:418–421.
2. Gilden DH, Wright RR, Schneck SA, et al. Zoster sine herpete, a clinical variant. Ann Neurol 1994;35:530–533.
3. Amlie-Lefond C, Mackin GA, Ferguson M, et al. Another case of virologically confirmed zoster sine herpete with electrophysiologic correlation. J Neurovirol 1996;2:136–138.
4. Okamoto Shigefumi, Hata A, Sadaoka K, et al. Comparison of varicella-zoster virus-specific immunity of patients with diabetes mellitus and healthy individuals. J Infect Dis 2009;200:1606–1610.
5. Heymann AD, Chodick G, Karpati T, et al. Diabetes as a risk factor for herpes zoster infection: results of a population based study in Israel. Infection 2008;36:226–230.
6. Hevner R, Vilela M, Rostomily R, et al. An unusual cause of trigeminal-distribution pain and tumour. Lancet Neurol 2003;2:567–572.
7. Mahalingam R, Traina-Dorge V, Wellish M, et al. Latent simian varicella virus reactivates in monkeys treated with tacrolimus with or without exposure to irradiation. J Neurovirol 2010;16:342–354.

Johanna Oechtering, MD
Gabor C. Petzold, MD

ACUTE HYDROCEPHALUS DUE TO IMPAIRED CSF RESORPTION IN TOSCANA VIRUS MENINGOENCEPHALITIS

Toscana virus, a neurotropic infectious agent endemic to Mediterranean countries, classified in the sandfly fever virus group (genus Phlebovirus, family Bunyaviridae), is a frequent cause of aseptic meningitis and encephalitis in Italy.[1] The disease usually has a favorable outcome, and reports of severe courses are rare.[1,2] We present an unusual case of acute hydrocephalus as the initial symptom of Toscana virus meningoencephalitis.

Case report. A 21-year-old student presented with a 36-hour history of progressive bifronto-temporal headaches, retroorbital pressure, fever, nausea, vomiting, and double vision due to bilateral sixth cranial nerve deficits.

Eight days before presentation, he had returned from a 2-week camping trip to Umbria, Italy, where he had suffered multiple tick bites. The patient's past personal and travel history was otherwise unremarkable. Apart from bilateral abductor nerve deficits, neurologic examination was normal, in particular showing no signs of meningism. Funduscopy showed neither papilledema nor venous pulsation. Neuropsychological and cognitive evaluation was normal. Physical examination was remarkable for mild splenomegaly. CT and MRI showed marked dilation of the lateral, third, and fourth ventricles (figure, A and B). T2-weighted sequences showed CSF flow void artifacts in the aqueduct (figure, C), indicating communicating hydrocephalus. There was no evidence for obstruction of the foramen of Monroe or aqueductal stenosis. MRI also showed scattered punctuate T2-hyperintense nonenhancing white matter lesions (figure, D). Magnetic resonance angiography was unremarkable, making cerebral venous thrombosis or vasculitis unlikely. Eight days after admission, CSF scintigraphy was performed for the differentiation between hypersecretory hydrocephalus and hydrocephalus due to impaired CSF resorption. This examination indicated pathologic reflux in the lateral ventricles, consistent with a blockage of CSF drainage in the subarachnoid space (figure, E).

Laboratory workup, including liver and kidney parameters, electrolytes, and full blood count, was unremarkable except for a mild elevation of C-reactive protein (1.03 mg/dL). Repeated CSF examination revealed moderate pleocytosis (figure, F) with normal