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Varicella zoster virus meningitis with hypoglycorrhachia in the absence of rash in an immunocompetent woman

Ali A Habib¹, Don Gilden², D Scott Schmid³, and Joseph E Safdieh¹

¹ Department of Neurology, New York Presbyterian Hospital Weill Cornell Medical College, New York, New York, USA

² Departments of Neurology and Microbiology, University of Colorado Denver School of Medicine, Aurora, Colorado, USA

³ National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Abstract

We report varicella-zoster virus (VZV) meningitis in a healthy adult woman with no antecedent rash and with hypoglycorrhachia. Cerebrospinal fluid (CSF) examination revealed the presence of VZV DNA, anti-VZV immunoglobulin G (IgG) antibody, and intrathecal production of anti-VZV IgG antibody.

Keywords

varicella zoster; meningitis; hypoglycorrhachia; PCR; immunocompetent

Case report

A 26-year-old healthy Bhutanese woman developed increasing throbbing bitemporal headache with photophobia, severe nausea, and vomiting over 2 days. She had been afebrile and denied neck stiffness. There was no past history of headache, skin rash, recent insect bite, or contact with individuals with infections. She had chickenpox at age 5 years. She had emigrated from Bhutan 7 years earlier, but had not traveled abroad recently. Her sister had been treated for tuberculosis. She worked currently as a nanny; the children under her care were healthy and had received Varivax months earlier. On examination, the patient was afebrile and had no rash, nuchal rigidity, or abnormal neurological signs.

On day 6 after becoming ill, white blood cell (WBC) count and routine blood chemistries, liver enzymes, erythrocyte sedimentation rate (ESR), anti-nuclear antibody, rapid plasma reagin, and human immunodeficiency virus testing were negative. Brain magnetic resonance imaging (MRI) revealed an ill-defined T2 hyperintensity in the right frontal lobe, extending from the cortical surface to the frontal horn of the lateral ventricle without mass effect, consistent with a hamartoma or cortical dysplasia. The cerebrospinal fluid (CSF) contained 331 WBCs, 99%

Address correspondence to Don Gilden, MD, Department of Neurology, Mail Stop B182, University of Colorado Denver School of Medicine, 12700 E. 19th Avenue, Aurora, CO 80045, USA. don.gilden@ucdenver.edu.

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mononuclear; CSF protein was 219 mg/dl, and there were no oligoclonal bands; CSF glucose was 28 mg/dl (serum glucose 75 mg/dl). She was treated with ceftriaxone, ampicillin, and intravenous acyclovir (10 mg/kg every 8 h) as well as rifampin, isoniazid, pyrazinamide, and ethambutol because of her history of tuberculosis exposure. Bacterial and viral cultures using MRC-5 primary monkey kidney and HEP-2 cells, acid fast bacillus smear and culture, and polymerase chain reaction (PCR) for mycobacteria were negative.

By day 8, her headache and associated symptoms resolved, and the remainder of her hospitalization was uncomplicated. All antibiotics were discontinued after bacterial culture and tuberculosis PCR were negative. A repeat MRI with gadolinium on day 10 was normal, with no change in the solitary T2 hyperintensity. A repeat CSF examination on day 13 revealed 108 WBCs, all mononuclear; CSF protein at 95 mg/dl and glucose at 39 mg/dl (serum glucose 88 mg/dl). She completed a 21-day course of intravenous acyclovir. A third CSF examination 1 month after the onset of symptoms did not reveal a pleocytosis; CSF protein was 46 mg/dl and glucose was 48 mg/dl (serum glucose 90 mg/dl).

Special studies

On day 6, PCR of the CSF revealed no amplifiable herpes simplex virus (HSV) or cytomegalovirus (CMV) DNA, but was positive for varicella-zoster virus (VZV) DNA (127,000 copies per ml CSF); studies for antiviral antibodies were not performed. On day 13, the CSF was negative for VZV DNA, but did contain anti-VZV IgG antibody. The serum/CSF ratio of anti-VZV immunoglobulin G (IgG) was 1.0 compared to a ratio of 52 for total IgG and 31 for albumin, and there was no anti-HSV IgG antibody in CSF, all consistent with intrathecal synthesis of anti-VZV IgG antibody. Because the second CSF did not contain VZV DNA, the third CSF obtained 1 month after onset of illness was not tested for VZV DNA, but was examined for anti-VZV IgG antibody, which was still present.

Discussion

We describe VZV meningitis in an immunocompetent adult woman with no antecedent zoster rash and with hypoglycorrhachia. Virological verification was provided by the detection of VZV DNA in CSF during acute disease and the detection of anti-VZV IgG antibody and intrathecal production of anti-VZV IgG antibody during convalescence. This report illustrates two notable features. First, it is the first case to show that PCR can detect VZV DNA in CSF during the first week of meningitis, followed by the disappearance of the DNA during the second week when anti-VZV IgG was found in CSF, the same pattern observed for HSV DNA and anti-HSV IgG antibody in patients with HSV encephalitis (Aurelius *et al*, 1991). In contrast, in patients with VZV vasculopathy, which is usually more protracted, anti-VZV IgG antibody is found in the CSF of all patients, compared to VZV DNA in only 30% of patients (Nagel *et al*, 2008). Overall, detection of VZV DNA in VZV meningitis and HSV DNA in HSV encephalitis reflects acute disease compared to chronic VZV vasculopathy when anti-VZV IgG antibody is always present and VZV DNA is present far less often. Second, the low level of CSF glucose in the presence of normal serum glucose levels in our patient was equal to the lowest ever reported in a 24-year-old man with thoracic zoster and aseptic meningitis whose CSF on day 5 showed glucose at 28 mg/dl; 4 days later, CSF glucose was 57 mg/dl (Wolf, 1974). Surprisingly, even on day 13, when our patient had improved clinically and viral DNA was no longer found in the CSF, glucose levels in CSF remained low.

Hypoglycorrhachia with VZV infection has been reported in zoster meningitis of immunocompetent adults (Echevarria *et al*, 1987; Moriuchi *et al*, 1997), even in the absence of rash (Mayo and Booss, 1989) and in children (Jhaveri *et al*, 2003; Leahy *et al*, 2008), as confirmed by PCR and serology. Hypoglycorrhachia has also been found in VZV

meningoencephalitis after ophthalmic distribution zoster (Reimer and Beller, 1981; Norris *et al*, 1970) and in zoster polyneuritis with no rash (Mayo and Booss, 1989).

In the past, VZV was considered to be a rare cause of viral meningitis. A survey of 368 patients with aseptic meningitis admitted to the Los Angeles County General Hospital in 1958 failed to identify VZV as a possible etiologic agent in any of these patients (Lennette *et al*, 1962), likely due to the techniques used to identify VZV, i.e., inoculation of stool cultures into monkey kidney cells and into 1-day-old mice. VZV isolation from CSF or stool is rare, and VZV is an exclusively human virus that does not produce disease after experimental infection of mice (Wroblewska *et al*, 1982). More recently, proof that VZV can cause serious neurological disease, often in the absence of rash, has been based on serologic analyses to detect VZV-specific antibodies (Shoji *et al*, 1976), as well as intracellular antigen in patients with zoster meningoencephalitis, cranial and spinal radiculoneuritis (Peters *et al*, 1979), and intrathecal production of anti-VZV antibodies (Martinez-Martin *et al*, 1985; Echevarria *et al*, 1987). Most recently, combined PCR and antibody testing revealed that VZV causes 5% to 27% of all aseptic meningitis (Koskiniemi *et al*, 2001; Hausfater *et al*, 2004; Kupila *et al*, 2006; Frantzidou *et al*, 2008), which is not altogether surprising because PCR has already shown that VZV causes zoster sine herpette (Gilden *et al*, 1994), vasculopathy (Gilden *et al*, 1996), acute (Gilden, 1994) and recurrent (Gilden *et al*, 2009) myelopathy, acute cerebellar ataxia (Moses *et al*, 2006; Ratzka *et al*, 2006), and retinal necrosis (el Azazi *et al*, 1991; Galindez *et al*, 1996), all without rash.

Viruses that can cause aseptic meningitis with hypoglycorrhachia include lymphocytic choriomeningitis virus (Jamieson *et al*, 1986) and mumps virus (Wilfert, 1969), as well as ECHO (Mirani *et al*, 1973) and Coxsackie (Marier *et al*, 1975) viruses in children. Now, VZV can be added to this list. PCR analysis, especially in the first week of acute symptoms of meningitis, with or without VZV rash, is essential in accurate diagnosis and treatment.

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