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Neurological Disease Produced by Varicella Zoster Virus Reactivation Without Rash

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Abstract

Reactivation of varicella zoster virus (VZV) from latently infected human ganglia usually produces herpes zoster (shingles), characterized by dermatomal distribution pain and rash. Zoster is often followed by chronic pain (postherpetic neuralgia or PHN) as well as meningitis or meningoencephalitis, cerebellitis, isolated cranial nerve palsies that produce ophthalmoplegia or the Ramsay Hunt syndrome, multiple cranial nerve palsies (polyneuritis cranialis), vasculopathy, myelopathy, and various inflammatory disorders of the eye. Importantly, VZV reactivation can produce chronic radicular pain without rash (zoster sine herpette), as well as all the neurological disorders listed above without rash. The protean neurological and ocular disorders produced by VZV in the absence of rash are a challenge to the practicing clinician. The presentation of these conditions varies from acute to subacute to chronic. Virological confirmation requires the demonstration of amplifiable VZV DNA in cerebrospinal fluid (CSF) or in blood mononuclear cells, or the presence of anti-VZV IgG antibody in CSF or of anti-VZV IgM antibody in CSF or serum.

1 Introduction

Varicella zoster virus (VZV) is an exclusively human neurotropic alphaherpesvirus. Primary infection causes varicella (chickenpox), after which virus becomes latent in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis. Years later, as cell-mediated immunity to VZV declines with age or immunosuppression, as in patients with cancer or AIDS or organ transplant recipients, VZV reactivates to cause zoster (shingles), a syndrome characterized by pain and a vesicular rash on an erythematous base in 1–3 dermatomes. Because VZV becomes latent in any and all ganglia, zoster can develop anywhere on the body. In most patients, the disappearance of skin lesions is accompanied by decreased pain and complete resolution of pain in 4–6 weeks. Nevertheless, zoster is often followed by chronic pain (postherpetic neuralgia) as well as meningitis or meningoencephalitis, cerebellitis, isolated cranial nerve palsies that produce ophthalmoplegia or the Ramsay Hunt syndrome (RHS), multiple cranial nerve palsies (polyneuritis cranialis), vasculopathy, myelopathy and various inflammatory disorders of the eye, the most common of which is progressive outer retinal necrosis (PORN). Importantly, VZV reactivation can produce chronic radicular pain without rash (zoster sine herpette), as well as all the neurological disorders listed above without rash – the subject of this chapter.

2 Zoster Sine Herpete

The concept of zoster without rash is not new and was initially suggested as a nosological entity by Widal (1907), who described a 38-year-old man with thoracic distribution pain, hyperesthesia, a dilated left pupil, a mononuclear pleocytosis in the cerebrospinal fluid (CSF), and a negative Wasserman test for syphilis. Serologic studies for VZV were not performed. Weber (1916) later described two patients with segmental pain and weakness who ultimately developed facial and truncal zoster. In the largest series of zoster sine herpete, 120 patients were described as experiencing “zoster-type” pain without rash in a dermatome distribution distant from a dermatome with rash (Lewis 1958). CSF examination revealed the modest mononuclear pleocytosis often encountered in patients with zoster, but serologic studies were not done.

The first serologic confirmation of zoster sine herpete was reported by a physician who developed acute trigeminal distribution pain that lasted 16 days and was associated with a rise in complement-fixing antibody to VZV from 1:8 on day 15 to 1:128 on day 32 and no rise in antibody to herpes simplex virus (HSV) (Easton 1970). Schott (1998) later reported four patients, who years after trigeminal distribution zoster, developed pain without rash in the same distribution of the trigeminal nerve; unfortunately, none were studied virologically. Virologic confirmation of zoster sine herpete did not come until the analysis of two men, ages 62 and 66 years, with thoracic-distribution radicular pain that had lasted for months to years without zoster rash. An extensive search for systemic disease and malignancy was negative. VZV DNA, but not HSV DNA, was found in the CSF of the first patient 5 months after the onset of pain, and in the second patient, 8 months after pain onset (Gilden et al. 1994a). After diagnosis, both men were treated successfully with intravenous acyclovir. A third virologically confirmed case of thoracic-distribution zoster sine herpete that persisted for years included the demonstration of frequent fibrillation potentials restricted to chronically painful thoracic root segments (Amlie-Lefond et al. 1996). In that case, the patient did not improve after treatment with intravenous acyclovir and oral famciclovir.

Although the nosologic entity of zoster sine herpete as a clinical variant has now been established, its prevalence will not be known until a greater number of patients with prolonged radicular pain have been studied virologically. Analysis should include both PCR to amplify VZV DNA in CSF and in blood mononuclear cells (MNCs), as well as a search for antibody to VZV in CSF. The latter, even in the absence of amplifiable VZV DNA, has been useful to support the diagnosis of vasculopathy and myelopathy produced by VZV without rash (Gilden et al. 1998). Analysis of serum anti-VZV antibody is of no diagnostic value in patients with prolonged pain, because such antibodies persist in nearly all adults throughout life, and the presence of serum antibodies to different VZV glycoproteins and non-glycosylated proteins is variable (Vafai et al. 1988). Zoster sine herpete is essentially a disorder of the peripheral nervous system (ganglioradiculopathy) produced by VZV without rash. VZV also produces disease of the CNS without rash (described below). At the University of Colorado, School of Medicine, we have encountered more cases of VZV infection without rash in the CNS than in the peripheral nervous system.

3 Preherpetic Neuralgia

The existence of ganglionitis without rash is supported by radicular pain preceding zoster, so-called preherpetic neuralgia. We studied six patients whose pain preceded rash by 7–100 days and was located in dermatomes different from as well as in the area of eventual rash (Gilden et al. 1991). Two patients ultimately developed disseminated zoster with neurologic complications of zoster paresis and fatal zoster encephalitis; both had been taking long-term low-dose steroids. A third case of preherpetic neuralgia developed in a patient with prior

metastatic carcinoma and a fourth was in a patient with an earlier episode of brachial neuritis. Two subjects had no underlying disease. Further documentation of preherpetic neuralgia will determine whether its apparent association with steroid therapy and serious complications is statistically significant.

4 Meningitis/Meningoencephalitis

Meningitis is characterized by headache, fever, and stiff neck. Additional impairment of higher cognitive function, alterations in state of consciousness, or seizures indicate underlying parenchymal involvement (encephalitis). VZV involvement of the CNS without rash was verified by the intrathecal synthesis of antibodies to VZV in two patients with aseptic meningitis (Martinez-Martin et al. 1985) and later in four additional patients with aseptic meningitis (Echevarria et al. 1987), and in one patient with acute meningoencephalitis (Vartdal et al. 1982). Powell et al. (1995) reported a patient with meningoencephalitis without rash whose CSF contained VZV DNA, and Mancardi et al. (1987) described a patient with encephalomyelitis without rash, in whom anti-VZV antibody was detected in the CSF. Most recently VZV meningitis with hypoglycorrhachia in the absence of rash developed in an immunocompetent woman (Habib et al. 2009).

5 Ramsay Hunt Syndrome

The strict definition of the RHS is peripheral facial nerve palsy accompanied by an erythematous vesicular rash on the ear (zoster oticus) or in the mouth. VZV causes the RHS. Some patients develop peripheral facial paralysis without ear or mouth rash associated with either a fourfold rise in antibody to VZV or the presence of VZV DNA in auricular skin, blood MNCs, middle ear fluid, or saliva (Hato et al. 2000). In a study of 32 patients with isolated peripheral facial palsy, Murakami et al. (1998) identified RHS zoster sine herpette in six (19%) of the patients based on a fourfold rise in serum antibody titer to VZV; four of these six patients were positive for VZV DNA by PCR when geniculate zone skin scrapings were studied. Further, Morgan and Nathwani (1992) found that 9.3% of Bell's palsy patients seroconverted to VZV, and Terada et al. (1998) found that blood MNCs from 4 of 17 Bell's palsy patients were positive for VZV DNA by PCR. Thus, a small proportion of "Bell's palsy patients" (idiopathic peripheral facial palsy) have RHS zoster sine herpette.

6 Polyneuritis Cranialis

There have been multiple instances of polyneuritis cranialis produced by VZV. The first report was of a 70-year-old man who seroconverted to VZV during acute disease (Mayo and Booss 1989). Another report described a 43-year-old man with acute polyneuritis cranialis who developed antibody in CSF to VZV but not to other human herpesviruses or to multiple ubiquitous paramyxoviruses or togaviruses (Osaki et al. 1995). Both men were immunocompetent. VZV-induced polyneuritis cranialis without rash has also been described in a patient with involvement of cranial nerves IX, X, and XI as well as upper cervical nerve roots without rash, and with anti-VZV antibody in the CSF (Funakawa et al. 1999).

7 Cerebellitis

While acute cerebellar ataxia (unsteadiness with or without tremor) is well-recognized as a potential complicating factor in childhood varicella (Connolly et al. 1994), there is one report of a child who became ataxic 5 days before chickenpox developed (Dangond et al. 1993). A virologically documented case of VZV cerebellitis without rash was in a 66-year-old man whose CSF at the time of presentation revealed mild lymphocytic pleocytosis and VZV DNA; 3 weeks later, anti-VZV IgG antibodies were detected in his CSF and additional analysis revealed intrathecal synthesis of anti-VZV IgG (Ratzka et al. 2006). A second case

of acute cerebellitis caused by VZV in the absence of rash occurred in a middle-aged, immunocompetent woman; virological analysis of her CSF revealed VZV DNA and anti-VZV IgG antibody (Moses et al. 2006). The primary clue that led to the request for virological tests for VZV in the CSF of this patient was the patient's early age of chickenpox. Interestingly, many individuals who develop zoster before age 60 had chickenpox before age 4 years (Kakourou et al. 1998; Chiappini et al. 2002). The reason that early chickenpox predisposes to early zoster remains unknown, but is reminiscent of the observation that many patients with subacute sclerosing panencephalitis, a chronic fatal encephalitis caused by measles virus, had measles before the age of 2 years.

8 Vasculopathy

Transient ischemic attacks and focal deficit are not uncommon after VZV reactivation. A prototype fatal case of chronic progressive vasculopathy of 314 days' duration in an immunocompetent 73-year-old-man (Case Records of the Massachusetts General Hospital; Case 5-1995) was virologically verified to be caused by VZV (Gilden et al. 1996). Nau et al. (1998) reported another case of VZV vasculopathy without rash with virological confirmation. Kleinschmidt-DeMasters et al. (1998) described an HIV-positive patient with fatal encephalomyelitis and necrotizing vasculitis without rash, pathologically verified to be caused by VZV. In the past two decades, there have been numerous reports of VZV vasculopathy without rash. In fact, the largest study of virologically confirmed cases of VZV vasculopathy revealed that more than one-third of patients did not have rash. Even in a virologically confirmed case of spinal cord infarction caused by VZV, rash did not occur until 3 days after the onset of myelopathy (Orme et al. 2007).

9 Myelopathy

Acute VZV myelopathy is usually characterized by paralysis in the legs, with bladder and bowel incontinence, and occurs in the absence of rash. Heller et al. (1990) initially described a 31-year-old immunocompetent man who developed transverse myelitis with partial recovery. Disease was attributed to VZV based on the development of antibody in CSF. Later, we encountered two patients with VZV myelopathy in the absence of rash (Gilden et al. 1994b). The first patient developed zoster followed by myelopathy 5 months later, when PCR-amplifiable VZV DNA was detected in CSF. The second equally fascinating patient developed myelopathy at the time of acute zoster. The myelopathy resolved, but recurred 6 months later. Five months after the recurrence of myelopathy, the patient's CSF contained both amplifiable VZV DNA as well as antibody to VZV. Another case of recurrent VZV myelopathy revealed anti-VZV IgG in CSF with reduced serum/CSF ratios of anti-VZV IgG at the time of recurrence in the absence of rash (Gilden et al. 2009). Overall, the spectrum of VZV myelopathy is broad, ranging from acute to chronic and rarely recurrent.

10 Ocular Disorders

An emerging body of literature describes multiple ocular inflammatory disorders produced by VZV in the absence of rash. VZV is the most common cause of PORN. Multiple cases of PORN caused by VZV in the absence of rash have been described (Friedman et al. 1993; Galindez et al. 1996). A case of severe unremitting eye pain without rash was proven to be caused by VZV based on the detection of VZV DNA in nasal and conjunctival samples (Goon et al. 2000). Other cases include third cranial nerve palsies (Hon et al. 2005), retinal periphlebitis (Noda et al. 2001), uveitis (Akpel and Gottsch 2000; Hon et al. 2005), iridocyclitis (Yamamoto et al. 1995), and disciform keratitis (Silverstein et al. 1997), all without rash and all confirmed virologically to be caused by VZV.

11 Remarkable Cases of VZV Infection Without Rash

Two remarkable cases of VZV infection without rash deserve mention. The first and most extreme example of VZV infection of the nervous system that we encountered was a 77-year-old man with T cell lymphoma and no history of zoster rash who developed meningo-radicularitis of the cranial nerve roots and cauda equina; he died 3 weeks after the onset of neurologic disease, confirmed pathologically and virologically to have been caused by VZV (Dueland et al. 1992). Autopsy revealed hemorrhagic inflammatory lesions with Cowdry A inclusions in the meninges and nerve roots, extending from cranial nerve roots to the cauda equina. The same lesions were present in the brain, although to a lesser extent. VZV antigen and nucleic acid, but not herpes zoster virus (HSV) or cytomegalovirus antigen or nucleic acid, were found in the infected tissue at all levels of the neuraxis. Thus, VZV should be included in the differential diagnosis of acute encephalomyelitis-adenopathy, particularly since antiviral treatment is available.

The second case was an immunocompetent 45-year-old woman with a 13-month history of right facial numbness and "lightning bolt-like" pain in the maxillary distribution of the right trigeminal nerve. Initially, numbness was present over the right side of the nose adjacent to the zygoma, and a light touch over this area or the right forehead produced pain (allodynia) over the entire face. Neurological examination revealed loss of pinprick sensation in the maxillary distribution of the right trigeminal nerve. Fifth nerve motor function and the corneal reflex were intact. The CSF was acellular. Brain scanning by both computerized tomography (CT) and MRI was normal. She was treated with neurontin, 900 mg three times daily, but her pain increased. One year later, both CT and MRI scans revealed a $0.9 \times 0.9 \times 2.0$ -cm homogeneously enhancing mass at the base of the right brain at the site of the trigeminal ganglion. There was never any history of zoster rash. The tumor was removed surgically. Pathological and virological analysis of the trigeminal ganglionic mass confirmed chronic active VZV-induced ganglionitis (Hevner et al. 2003).

12 Systemic Disease Produced by VZV Reactivation Without Rash

Ross et al. (1980) reported a case of fatal hepatic necrosis caused by VZV in a 64-year-old woman. She had undergone splenectomy 14 months before the fatal hepatitis. The postmortem diagnosis was based on characteristic pathological changes in the liver, the detection of herpesvirus virions in liver by electron microscopy, and serologic evidence of recent VZV infection. A report of fulminant fatal disseminated VZV infection without rash occurred in an 8-year girl undergoing chemotherapy for leukemia; virus was present in blood, lungs, liver, kidneys, and bone marrow (Grant et al. 2002). Although the nervous system was spared in both patients, these cases confirm the existence of disseminated VZV infection of multiple organs in the absence of rash.

13 Subclinical VZV Reactivation

All of the above reports support the notion that VZV can reactivate to produce neurological and systemic disease without a characteristic zosteriform rash. VZV also reactivates subclinically. Ljungman et al. (1986) demonstrated subclinical reactivation in 19 of 73 (26%) bone marrow transplant recipients, as determined by a fivefold increase in VZV-specific antibody titers or a reappearance of a specific lymphoproliferative response to VZV antigen. Only 2 of the 19 patients with VZV reactivation had signs: one experienced transient fever, and the other developed hepatitis simultaneously with increasing VZV titers. Serologic analysis has also indicated VZV as the cause of unexplained fever in three of nine metastatic breast cancer patients (Rasoul-Rockenschaub et al. 1990). In addition, VZV reactivates subclinically (without pain or rash) in astronauts (Mehta et al. 2004), including shedding of infectious virus (Cohrs et al. 2008), most likely reflecting transient stress-

induced depression of cell-mediated immunity to VZV (Taylor and Janney 1992). Importantly, asymptomatic shedding of human neurotropic alphaherpes-viruses is not restricted to VZV, since HSV-1 (Kaufman et al. 2005) and HSV-2 (Koelle et al. 1992) also show subclinical reactivation. Finally, VZV DNA has been detected in saliva of patients with zoster in multiple dermatomes (Mehta et al. 2008), suggesting the simultaneous reactivation of VZV not only from geniculate ganglia but also from ganglia corresponding to the dermatome where zoster occurred. Detection of VZV DNA in saliva of such zoster patients provides a virological explanation for the classic clinical observations of Lewis (1958) who described dermatomal distribution radicular pain in areas distinct from pain with rash. Such clinical and virological phenomena are not surprising, since VZV becomes latent in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis.

14 Diagnostic Testing

While zoster is usually diagnosed based on observation alone, all neurological complications of VZV reactivation without rash require virological confirmation. Evidence of active VZV infection is supported by any or all of the following positive tests: the presence of anti-VZV IgM antibody in serum or CSF or anti-VZV IgG antibody in CSF, or the detection of VZV DNA in blood MNCs or CSF. Because nearly all adult serum contains anti-VZV IgG antibody, serological testing for anti-VZV IgG antibody alone without other virological testing is of no value. In our experience, the most valuable tests are those that detect VZV DNA or anti-VZV IgG antibody in CSF. Much less frequently, anti-VZV IgM is found in serum or CSF, and even less often, VZV DNA is found in blood MNCs during acute neurological disease. Some, but not all, clinical hospital laboratories either perform tests for anti-VZV IgG antibody or send the specimen to an outside laboratory. If the hospital cannot conduct a test for anti-VZV IgG or IgM antibody, the referring hospital cannot conduct a test for anti-VZV IgG or IgM antibody, the referring physician should contact Dr. Don Gilden (don.gilden@ucdenver.edu) who will arrange to have the specimen tested at no cost to the patient. Because VZV DNA was found in the saliva of every zoster patient in the study by Mehta et al. (2008), it is possible that saliva may be a useful source to detect VZV in patients with neurological disease in the absence of rash. To date, definitive virological confirmation has required blood and CSF examination for VZV DNA and anti-VZV IgM and/or IgG antibody. The continuing challenge for the clinician is in establishing a diagnosis at a time when treatment will still benefit the patient.

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Abbreviations

AIDS	Acquired immune deficiency syndrome
CSF	Cerebrospinal fluid
CT	Computerized tomography
HSV	Herpes simplex virus
Ig	Immunoglobulin
MNCs	Mononuclear cells

MRI	Magnetic resonance imaging
PORN	Progressive outer retinal necrosis
RHS	Ramsay Hunt syndrome
SSPE	Subacute sclerosing panencephalitis
VZV	Varicella zoster virus

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