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The protean manifestations of varicella-zoster virus vasculopathy

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Varicella-zoster virus (VZV) vasculopathy in the central nervous system (CNS) affects large and small cerebral vessels. Large-vessel disease is most common in immunocompetent individuals, whereas small-vessel disease usually develops in immunocompromised patients. In some patients, both large and small vessels are involved. Neurological features are protean. Neurological disease often occurs months after zoster and sometimes without any history of zoster rash. Magnetic resonance imaging (MRI) scanning, cerebral angiography, and examination of cerebrospinal fluid (CSF) with virological analysis are needed to confirm the diagnosis. VZV vasculopathy patients do not always have VZV DNA in CSF, but diagnosis can be confirmed by finding anti-VZV antibody in CSF, along with reduced serum/CSF ratios of VZV immunoglobulin G (IgG) compared to albumin or total IgG. When VZV vasculopathy develops months after zoster, antiviral treatment is often effective. *Journal of NeuroVirology* (2002) **8(suppl. 2),** 75–79.

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Varicella-zoster virus is highly neurotropic and produces disease of the peripheral and central nervous system

Varicella-zoster virus (VZV) is an exclusively human neurotropic alphaherpesvirus. Primary infection produces ~4 million cases of chickenpox annually. After chickenpox, VZV becomes latent in cranial nerve, dorsal root, and autonomic nervous system ganglia along the entire neuraxis. Virus reactivation, most common in elderly and immunocompromised individuals, produces zoster (shingles). Zoster is characterized by severe, sharp, lancinating radicular pain and rash restricted to one to three dermatomes. In more than 40% of zoster patients over age 60, pain persists for months and sometimes years, so-called postherpetic neuralgia (PHN). Although the pain of zoster and the more chronic pain of PHN are difficult to manage, neither is life-threatening. Less often, when VZV reactivates from ganglia, virus spreads to arteries of the brain and spinal cord and produces a vasculopathy that affects large and small cerebral vessels. Compared to zoster and PHN, VZV vasculopathy is more serious, producing considerable neurologic deficit and sometimes death.

This review describes the clinical, laboratory, and brain imaging features of the various vasculopathies produced by VZV. Multiple cases described in the literature by us and others are included to provide a perspective of VZV vasculopathy. We emphasize the protean clinical manifestations of neurological disease produced by VZV vasculopathy, as well as the importance of using both polymerase chain reaction (PCR) to amplify VZV DNA in cerebrospinal fluid (CSF) and analysis of antiviral antibody titers to VZV in both CSF and serum to aid in diagnosis, particularly when rash precedes the onset of neurological disease by months or is absent altogether.

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Large- and small-vessel vasculopathies can develop after either zoster or varicella and indicate active VZV infection

VZV large-artery disease (also known as granulomatous arteritis) predominates in elderly immunocompetent adults and is characterized by an acute focal deficit that develops weeks to months after contralateral trigeminal distribution zoster (Rosenblum and Hadfield, 1972; Bourdette *et al*, 1983), and rarely without a history of zoster (Nau *et al*, 1998). Vasculopathy is usually restricted to one to three arteries in the anterior, circulation (mostly the carotid, anterior, and middle cerebral arteries). Unifocal large vessel vasculopathy has also been described in children with varicella (chickenpox), thus making VZV one cause of acute infantile hemiplegia (Kamholz and Tremblay, 1985; Leopold, 1993). Pathological and virological analysis of affected arteries from cases of clinically unifocal vasculopathy after zoster or varicella reveals multinucleated giant cells, Cowdry A inclusion bodies, and herpesvirus particles (Fukumoto *et al*, 1986), as well as VZV DNA and antigen (Figure 1) in affected vessels (Gilden *et al*, 1996; Melanson *et al*, 1996). In protracted cases, virus may penetrate into cerebral parenchyma.

VZV infection of smaller cerebral blood vessels produces a combination of headache, fever, mental status changes and multifocal deficit, evident on neurological examination and by brain magnetic resonance imaging (MRI) (Figure 2). A CSF mononuclear pleocytosis is characteristic. Small-vessel infection occurs most often, although not exclusively, in immunocompromised individuals with zoster. Most patients have acquired immunodeficiency syndrome (AIDS) or have been immunosuppressed after organ transplantation or by chemotherapy for cancer. Disease is frequently protracted and may develop without zoster rash. Both ischemic and hemorrhagic infarcts are found in cortical as well as subcortical gray and white matter (Amlie-Lefond *et al*, 1995; Kleinschmidt-DeMasters *et al*, 1996). VZV multifocal vasculopathy has also been described after varicella. A recent report by Häusler *et al* (2002) of neurological disease in patients with varicella documented the multifocal nature of central nervous system (CNS) involvement and confirmed that VZV had produced the vasculopathy by an antiviral antibody titer assay. The

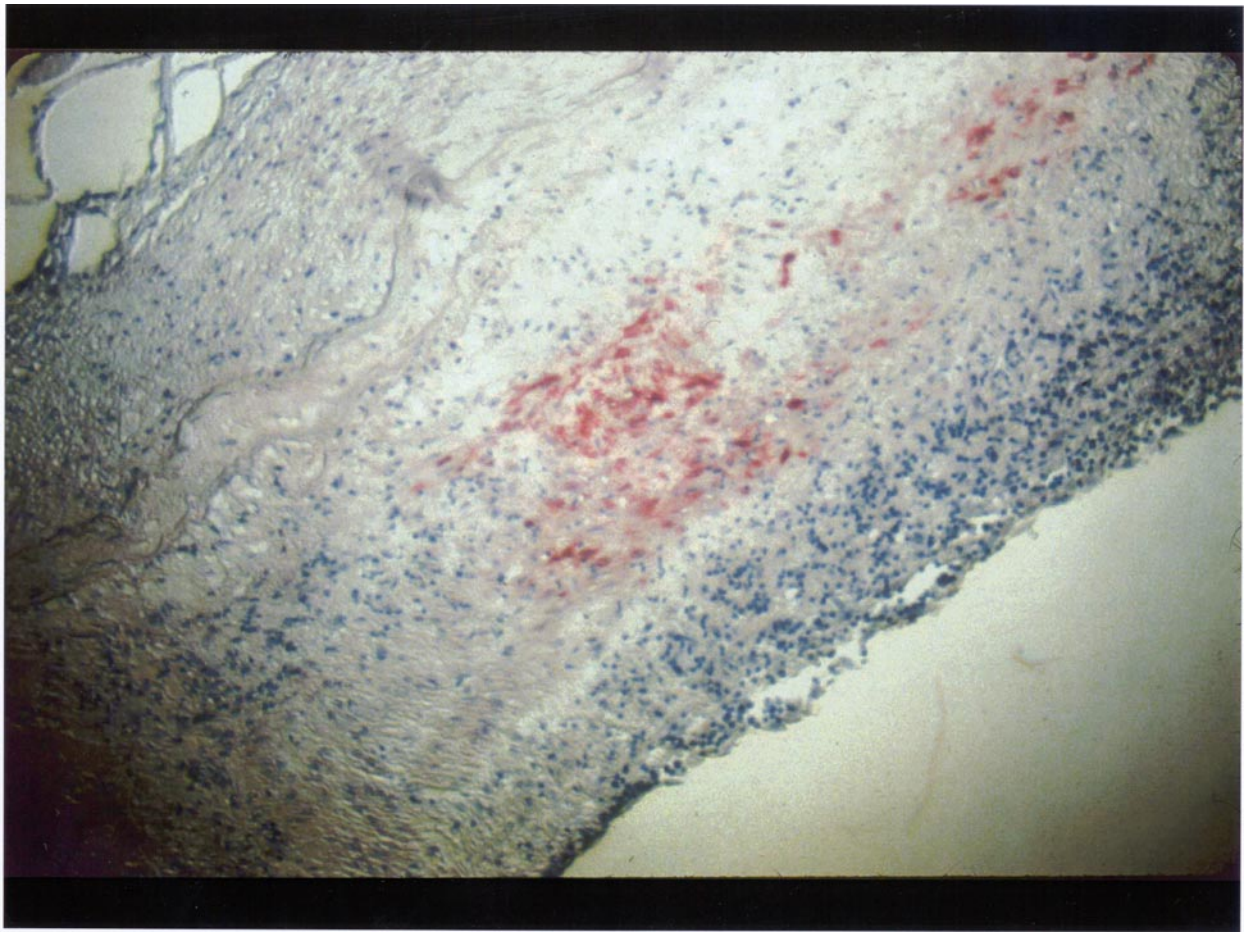

Figure 1 Immunohistochemical analysis of cerebral artery from a patient with VZV vasculopathy. VZV antigen (red staining) is detected after incubation of artery with rabbit antiserum again the VZV open reading frame (ORF) 63 protein. ×86.

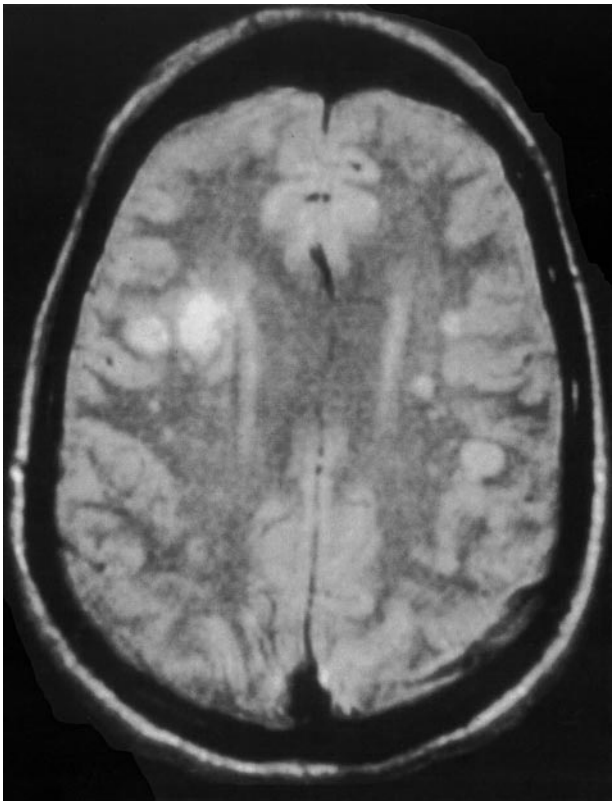

Figure 2 VZV multifocal vasculopathy. Proton-density brain MRI scan shows multiple areas of infarction in both hemispheres, particularly involving white matter and extending to gray-white matter junctions.

importance of antiviral antibody titers to diagnose VZV infection of both the central and peripheral nervous systems, even in the absence of amplifiable VZV DNA, has been emphasized (Gilden *et al*, 1998; Fox *et al*, 2001). Proof that VZV multifocal vasculopathy occurs after varicella is consistent with both cranial axial tomography (CAT) and MRI findings of bilateral infarction in brains of children with varicella who developed serious neurological disease (Darling *et al*, 1995).

VZV vasculopathy can develop months after rash or entirely without rash

Numerous cases of VZV vasculopathy in immunocompetent and immunocompromised individuals without rash have been described. One prototype subject was a 73-year-old immunocompetent man with headache, fever, mental status changes and focal deficit, and no history of zoster. His neurological symptoms and signs developed over 20 days. Repeated CSF examinations revealed persistent pleocytosis of both white blood cells (predominantly mononuclear) and red blood cells. Brain MRIs revealed multiple superficial and deep infarcts in central gray and white matter and brainstem, and angiography showed focal narrowing in the internal carotid, anterior, and middle cerebral arteries. The patient died. A diagnosis of vasculopathy without a specific cause was made. Postmortem analysis of brain and arteries revealed VZV DNA and antigen in two arteries around the circle of Willis, but not in brain (Gilden *et al*, 1996). The importance of this case is that it emphasized the involvement of both large and small arteries in an immunocompetent individual, that disease was protracted and developed in the absence or rash, and that vasculopathy was produced by active VZV infection in cerebral arteries.

Another patient was a 71-year-old man with chronic lymphocytic leukemia in remission who developed bilateral sacral distribution zoster. One month later, he developed headache, confusion, and an unsteady gait. Although brain MRI and magnetic resonance angiography (MRA) were normal, two CSF examinations revealed a mononuclear pleocytosis. VZV DNA was not detected in his CSF. His symptoms resolved in 2 months. Six months later, he developed dysphasia and focal left-sided signs. A brain MRI revealed a right pericallosal-distribution infarct, and MRA revealed right anterior cerebral artery occlusion and left anterior cerebral artery stenosis. Although the CSF was acellular, total immunoglobulin G (IgG) was increased and there were 3–4 oligoclonal bands. No VZV DNA was found, but his VZV IgG antibody titer was extraordinarily high in the CSF. Furthermore, the serum/CSF VZV IgG ratio was reduced compared to ratios for total IgG and albumin, consistent with intrathecal synthesis of anti-VZV antibody (Reiber and Lange, 1991). This case illustrated the development of acute unifocal (pericallosal) VZV vasculopathy remote from the original sacral distribution zoster, most likely attributable to reactivation of VZV from both trigeminal ganglia and spread to the anterior cerebral arteries. Even when VZV vasculopathy develops 6 months after zoster, antiviral treatment is effective (Gilden *et al*, 2002).

Another case of pure small vessel vasculopathy developed in an immunocompetent 76-year-old woman. Six months after left ophthalmic-distribution zoster, she developed ipsilateral loss of vision and, on examination, had bare light perception and a pale optic nerve without retinal pallor, edema, or a cherry-red spot. Although VZV DNA was not detected in her CSF, there was increased VZV IgG antibody in the CSF and reduced serum/CSF ratios of VZV IgG compared to serum/CSF ratios for total IgG and albumin. She was successfully treated with antiviral agents. This case of acute VZV posterior ischemic optic neuropathy further underlines the fact that vasculopathy can develop months after zoster and is still eminently treatable (Gilden *et al*, 2002).

Most recently, we encountered a human immunodeficiency virus–infected patient who had progressive CNS disease for more than 3 months (Kronenberg *et al*, 2002). Brain MRIs revealed multiple superficial and deep infarcts. MRA was normal. Both VZV DNA

and antibody were detected in CSF with reduced serum/CSF ratios of VZV IgG compared to total IgG and albumin. Serial PCR analyses of CSF confirmed the presence of persistent VZV DNA, clinched the diagnosis of VZV multifocal vasculopathy, and guided the duration of therapy. Five months later, the neurological examination was normal. The patient never had zoster rash.

The nomenclature of VZV CNS infection needs revision

As the nomenclature of clinical unifocal and multifocal VZV vasculopathy becomes appreciated, it is important to recognize that syndromes of large- and small-vessel vasculopathy are not always distinct. Both may be involved and produce waxing and waning neurological symptoms and signs. In that context, the designation "VZV unifocal or multifocal vasculopathy," rather than "VZV encephalitis," seems appropriate because the symptoms and signs seen clinically and on brain imaging indicate vasculopathy rather than encephalitis. Prompt recognition by clinicians of a unifocal or multifocal vasculopathy after zoster or varicella should lead to improved diagnosis and rapid treatment.

Other VZV infection without rash

In addition to vasculopathy, VZV may cause disease at multiple levels of the neuraxis involving the central and peripheral nervous system in the absence of rash. We reported an extraordinary case of encephalomyeloradiculoneuropathy in an immunocompromised patient (Dueland *et al*, 1991). The clinical picture resembled Guillain-Barré syndrome in that the patient developed acute flaccid quadriplegia and multiple cranial neuropathies, with a CSF protein of 2232 mg %. Some signs of CNS involvement were present (confusion and crossed abductor reflexes), but brain involvement was not diagnosed until autopsy, which revealed widespread VZV infection of brain, spinal cord, ganglia, and nerve roots along the entire neuraxis as well as VZV in multiple visceral organs. No zoster rash developed at any time.

We have also described cases of acute, chronic, and recurrent neuropathy, all without rash (Fox *et al*, 2001) and myelopathy (Gilden *et al*, 1994; de Silva *et al*, 1996), some without rash, caused by VZV based on detection of VZV DNA and VZV antibody in CSF, along with reduced serum/CSF ratios of VZV IgG compared to total IgG or albumin, or both. Some of these patients responded well to treatment with intravenous acyclovir, underscoring the value of aggressive testing for VZV in unusual cases of neuropathy.

Overall, VZV is a neurotropic virus that infects CNS blood vessels of various calibers, producing protean multifocal or unifocal neurological disorders. Diagnosis requires recognition by clinicians of the diversity of syndromes that can be caused by VZV, a high index of suspicion, and extensive testing for VZV DNA and antibody in CSF. Finally, nearly all CNS disease caused by VZV infection entail stroke, and infarction may follow zoster or varicella. Disease is not a primary encephalitis, but instead due to unifocal or multifocal infarction that develops secondary to productive virus infection within large and small cerebral arteries. Rarely, VZV is associated with disseminated encephalomyelitis, a CNS complication of chickenpox. These issues are discussed in greater detail in Gilden (2002).

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