Review Article

Varicella Zoster Virus: A Common Cause of Stroke in Children and Adults

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Background: Varicella zoster virus (VZV) is a neurotropic, exclusively human herpesvirus. Primary infection causes varicella (chickenpox), after which the virus becomes latent in ganglionic neurons along the entire neuraxis. As cell-mediated immunity to VZV declines with advancing age and immunosuppression, VZV reactivates to produce zoster (shingles). One of the most serious complications of zoster is VZV vasculopathy. *Methods:* We reviewed recent studies of stroke associated with varicella and zoster, how VZV vasculopathy is verified virologically, vaccination to prevent varicella and immunization to prevent zoster, and VZV in giant cell arteritis (GCA). *Findings:* We report recent epidemiological studies revealing an increased risk of stroke after zoster; the clinical, laboratory, and imaging features of VZV vasculopathy; that VZV vasculopathy is confirmed by the presence of either VZV DNA or anti-VZV IgG antibody in cerebrospinal fluid; special features of VZV vasculopathy in children; vaccination to prevent varicella and immunization to prevent zoster; and the latest evidence linking VZV to GCA. *Conclusion:* In children and adults, VZV is a common cause of stroke. **Key Words:** VZV—vasculopathy—stroke—giant cell arteritis.

Introduction

Varicella zoster virus (VZV) is a neurotropic alphaherpesvirus. Primary infection, usually in childhood, causes varicella (chickenpox), after which the virus becomes latent in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis.[1] As cell-mediated immunity to VZV declines with advancing age and immunosuppression, VZV reactivates to produce herpes zoster (shingles), frequently complicated by postherpetic neuralgia (PHN, radicular pain that persists long after the disappearance of rash). Zoster is also complicated by meningoencephalitis, myelitis, multiple serious ocular disorders, and VZV vasculopathy. Importantly, all of the neurological and ocular complications of zoster may develop in the absence of rash. Diagnosis is confirmed either by the presence of VZV DNA or anti-VZV antibodies in cerebrospinal fluid (CSF). Rapid virological verification and prompt treatment with antiviral agents can lead to complete recovery, even in patients with protracted disease.

Overview

VZV vasculopathy occurs in adults and children. Patients present with both transient ischemic attacks (TIAs) and stroke. Less often, patients present with subarachnoid or intracerebral hemorrhage secondary to ruptured aneurysm. The disease is often waxing and waning.

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Received March 11, 2016; accepted March 27, 2016.

Grant support: This work was supported by a grant from the National Institutes of Health (grant no. AG032958) to D.G.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.03.052

Multiple cases of protracted disease that lasted for more than 1 year have been described. Both large and small arteries are affected. The characteristic pathology of VZV vasculopathy matches that of granulomatous arteritis. Virological analysis of intracerebral arteries of patients who died of VZV vasculopathy reveals Cowdry type A inclusion bodies, multinucleated giant cells, herpes virions, VZV DNAs, and VZV antigens, indicating productive arterial infection by VZV. Interestingly, VZV is the only human virus that has been shown to replicate in cerebral arteries and produce disease.

Stroke after Zoster

In the past few years, multiple epidemiological studies from Taiwan, Europe, the United Kingdom, and the United States have shown that the incidence of stroke in patients with a recent history of zoster is greater than in age-matched control patients. Analysis of Taiwanese National Health Research Institute records revealed a 30% increased risk within 1 year after zoster,[2] increasing 4.5-fold with ophthalmic-distribution zoster.[3] A similar analysis of the Danish National Registry revealed a 126% increased risk of stroke within 2 weeks after zoster, a 17% increased risk from 2 weeks to 1 year after zoster, and a 5% increased risk of stroke after the first year.[4] Studies from the U.K. Health Improvement Network general practice database showed not only that the risk of TIAs increased 1.15-fold but also that myocardial infarctions (MIs) were increased 1.10-fold after zoster; and in zoster patients under 40 years of age, the risk for stroke, TIAs, and MIs was significantly higher (1.74-, 2.42- and 1.49-fold, respectively).[5] A study from the U.K. Clinical Practice Research Datalink showed that the risk of stroke after zoster decreased over time in all dermatomes, with a statistically significant age-adjusted incidence of 1.63 at 1-4 weeks, 1.42 at 5-12 weeks, and 1.23 at 13-26 weeks after zoster, but no decrease at later times.[6] In patients with ophthalmic-distribution zoster, the risk of stroke was increased 3-fold at 5-12 weeks after zoster. Finally, among 55% of zoster patients who received oral antiviral therapy, the stroke risk was reduced compared to that in untreated zoster patients, indicating the value of antiviral treatment in reducing stroke incidence after zoster.

More recently, a register-based cohort study in Sweden showed a 1.34-fold increased risk of stroke within 1 year after zoster in all age groups.[7] As in the U.K. study, the risk of stroke in patients 39 years and younger was increased 10.3-fold within 1 year after zoster. Another U.K. study showed that the risk of stroke and MI increased 2.4- and 1.7-fold, respectively, within 2 weeks after zoster.[8] Finally, in the first U.S. population-based study, the risk of stroke within 3 months of zoster was reportedly increased 1.53-fold.[9] While stroke in the pediatric population is less common, approximately one third of arterial ischemic stroke is associated with varicella,[10] with 44% of transient cerebral arteriopathy preceded by varicella.[11] Together, these studies show that varicella and zoster are risk factors for stroke, particularly in individuals who develop zoster under 40 years of age, and that antiviral therapy may decrease this risk.

Pathophysiology of VZV Vasculopathy

After zoster, most commonly after ophthalmic-distribution zoster or even in the absence of rash, intracerebral arteries likely become infected when virus that has reactivated from trigeminal or other cranial nerve ganglia spreads transaxonally. Decades ago, application of horseradish peroxidase to the external surface of the carotid and intracranial circulation, including the venous sinuses, of cats revealed that intracerebral arteries and veins receive a rich supply of trigeminal afferent fibers.[12,13] After VZV reaches the arterial adventitia, virus spreads transmurally to infect all layers of the cerebral arteries, resulting in the characteristic pathology of granulomatous arteritis. Virological and immunological analyses of VZV-infected arteries have revealed disruption of the internal elastic lamina and progressive intimal thickening, with cells expressing smooth muscle actin but decreased smooth muscle cells in the media.[14] The pathophysiology of VZV vasculopathy appears to be similar in children. Histopathology of the middle cerebral artery (MCA) of a 4-year-old girl who died of VZV vasculopathy revealed granulomatous arteritis with multinucleated giant cells, extensive lymphocytic infiltration, and VZV antigen, primarily in the smooth muscle layer.[15]

Clinical, Laboratory, and Imaging Features of VZV Vasculopathy

The onset of stroke or TIAs in elderly patients with a history of zoster or in children with varicella in recent months should alert clinicians to the possibility of VZV vasculopathy. Whereas most VZV vasculopathies develop within 6 weeks after zoster, the median interval for stroke after varicella is 4 months.[16] Besides stroke and TIAs, patients may develop severe headache, cognitive impairment/confusion, or unsteadiness. Again, VZV vasculopathy in adults is often protracted. Cases that lasted 1 year before death[17] or that were confirmed virologically after 6 or 12 months of waxing and waning disease, including a favorable response to antiviral treatment, are well documented.[18,19] Computed tomography or magnetic resonance imaging (MRI) scanning often reveals a single or multiple areas of ischemia/infarction in the distribution of large or small arteries and often both. In patients with multifocal VZV vasculopathy, lesions at gray–white matter junctions, along with deep-seated and cortical infarction, are common. Such a pattern leads the neuroradiologist