

Varicella Zoster Virus Infection: Generally Benign in Kids, Bad in Grown-ups

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(See the Major Article by Langan et al on pages 1497–503.)

Keywords. stroke; giant cell arteritis.

Varicella zoster virus (VZV), an exclusively human neurotropic double-stranded DNA virus, is 1 of 8 human herpesviruses. Primary infection causes varicella (chicken pox), after which virus becomes latent in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis. As VZV-specific cell-mediated immunity declines in elderly individuals, as well as in patients with AIDS and other immunocompromising conditions, VZV reactivates from 1 or more ganglia to cause herpes zoster (shingles). Zoster is frequently complicated by chronic pain (postherpetic neuralgia) as well as meningoencephalitis, cerebellitis, myelitis, VZV vasculopathy, and multiple ocular disorders. Among the most debilitating and life-threatening complications of zoster is VZV vasculopathy, a cause of transient ischemic attack (TIA) and stroke.

Historically, VZV vasculopathy was known to present as acute hemiplegia

after contralateral herpes zoster ophthalmicus or as a postvaricella arteriopathy in children. However, in recent years, the clinical spectrum of VZV vasculopathy has expanded to include TIA, ischemic stroke, and hemorrhagic stroke often involving both large and small vessels, multifocal VZV vasculopathy with temporal artery infection mimicking giant cell arteritis, extracranial vasculopathy, aneurysm with and without subarachnoid hemorrhage, arterial dissection and dolichoectasia, ischemic cranial neuropathy, cerebral venous sinus thrombosis, spinal cord infarction, and peripheral thrombotic disease.

VZV is the only human virus that has been proven to replicate in cerebral arteries and produce stroke. Studies of the pathogenesis of disease reveal that upon reactivation from ganglia, VZV travels transaxonally to the adventitia of arteries where productive infection is established, followed by transmural migration of virus to the arterial media and intima, pathological vascular remodeling, and stroke. The notion that virus spreads transaxonally after reactivation from trigeminal and other cranial nerve ganglia is supported by the demonstration of afferent fibers from trigeminal ganglia to intracranial blood vessels, venous sinuses, and dural structures [1, 2]. Evidence for productive VZV infection of affected arteries was first provided by virologic analysis of a patient who died after VZV

vasculopathy; the infected arteries contained Cowdry A inclusion bodies, multinucleated giant cells, herpes virions, and both VZV DNA and antigen [3].

The mechanism(s) by which VZV causes pathological vascular remodeling can be surmised from studies of VZV-infected arteries from patients with virologically confirmed VZV vasculopathy. Immunohistochemical analyses using antibodies directed against VZV, endothelium, and smooth muscle actin and myosin revealed the presence of VZV antigen in the outermost arterial layer (adventitia) early in infection and later in the media and intima layers, consistent with both transaxonal spread of reactivated VZV to the arterial adventitia followed by transmural spread of virus [4]. Moreover, virus-infected arteries revealed a disrupted internal elastic lamina, a thickened intima composed of cells expressing α smooth muscle actin and smooth muscle myosin heavy chain, but not endothelial cells expressing CD31 and decreased numbers of medial smooth muscle cells [4]. The loss of medial smooth muscle cells and the presence of cells expressing myosin in the thickened intima suggest that some of these latter cells are of medial smooth muscle origin.

A follow-up study of inflammatory cells and their distribution in normal cerebral arteries and in VZV-infected arteries at 3 days after onset of disease (early

Received 4 February 2014; accepted 5 February 2014; electronically published 2 April 2014.

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Clinical Infectious Diseases 2014;58(11):1504–6

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DOI: 10.1093/cid/ciu099

and 10 months after protracted neurologic disease (late) [5] revealed CD4⁺ and CD8⁺ T cells, CD68⁺ macrophages, and rare CD20⁺ B cells throughout the arterial adventitia and intima, but not in the media [5]. Early VZV vasculopathy was distinguished by the presence of abundant neutrophils in the adventitia that were absent in late VZV vasculopathy. In late VZV vasculopathy, viral antigen was seen in the media in the absence of leukocytes, supporting the notion that the media is an immunoprivileged site [6]. Inflammatory cells were absent in control arteries. Finally, a thickened intima was associated with inflammation in vasa vasorum vessels in early VZV vasculopathy, consistent with a role for virus-induced inflammation in vessel wall remodeling [7, 8].

Together, the findings point to the role of altered arterial caliber and contractility, produced in part by abnormal accumulation of smooth muscle cells and myofibroblasts in the thickened neointima and by disruption of the media associated with the presence of viral antigen and inflammatory cells, in VZV-associated stroke.

Although the exact incidence of VZV vasculopathy is unknown, recent studies from the United Kingdom, Europe, and Asia have indicated that stroke after zoster is not uncommon. A study of 7760 adults with zoster and 23 280 matched controls without zoster that analyzed medical records from the Taiwan National Health Research Institute revealed a 30% increased risk of stroke in the year after zoster, a risk that was further increased 4-fold when zoster was in the ophthalmic division of the trigeminal nerve [9]. Use of the same database for additional analysis of 658 individuals with ophthalmic-distribution zoster and 1974 controls confirmed a 4.5-fold increased risk of stroke in the year after zoster in the former group compared with controls and no found effect of antiviral treatment on the difference in rates [10]. Some limitations of the 2 studies included

key confounders such as body mass index and atrial fibrillation, and the analysis of the risk of stroke at only a single time-point (1 year after zoster).

Analysis of medical records from a Danish national registry of 4.6 million adults, of whom 117 926 were zoster patients treated with antiviral therapy, 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 compared with the control group of untreated zoster patients [11]. Limitations of this study included the use of antiviral treatment as a proxy for zoster, which may have resulted in false-positive exposures as some people with herpes simplex virus infection may have received treatment. Furthermore, controls were inadequate for confounders.

Most recently, the UK Health Improvement Network general practice database was used to analyze 106 601 cases of zoster and 213 202 controls matched for age, sex, and general practice and found a statistically significant increase in TIA and myocardial infarctions (MI) in patients with zoster; importantly, the increased risk was greatest in zoster patients <40 years of age [12]. The cohort design of that study raises the possibility of confounding by individual differences in the zoster and control group. Moreover, the increased stroke risk at various time periods after zoster was not examined.

In this issue of *Clinical Infectious Diseases*, Langan and colleagues present the latest results on the risk of stroke after zoster [13]. The UK General Practice Research Database (1987–2012) was used to analyze 6584 individuals with a first-ever diagnosis of zoster associated with stroke before and after rash. For each individual in the self-controlled case-series method, the incidence of stroke from the time of zoster until 1 year later was compared with 2 control periods: (1) the time of enrollment in the study until 1 month before zoster; and (2) from 1 year after zoster until the end of the study period.

Age-adjusted incidence ratios and 95% confidence intervals were calculated. The results showed that stroke risk decreased over time after zoster in any dermatome as compared to the control time periods. Statistically significant age-adjusted incidence ratios of stroke were found 1–4 weeks after zoster (1.63), 5–12 weeks after zoster (1.42), and 13–26 weeks after zoster (1.23), with no increase at later times. In patients with ophthalmic-distribution zoster, the risk of stroke was increased 3-fold from 5 to 12 weeks after zoster. Finally, among the 55% of zoster patients who received oral antiviral therapy, the risk of stroke was reduced compared with untreated patients with zoster. Overall, results of the novel self-controlled case series method confirmed studies from Taiwan, Denmark, and the earlier UK study that revealed an increased risk of stroke after zoster, particularly in patients with ophthalmic-distribution zoster. Furthermore, the current study is the first to show that the increased risk of stroke after zoster can be reduced with antiviral treatment.

It should be noted that VZV infection is not limited to intracranial cerebral arteries. In the past 2 years, VZV infection was demonstrated in extracranial temporal arteries in 3 patients. The first case was in an elderly man who developed ophthalmic-distribution zoster, followed 1 month later by multifocal VZV vasculopathy that manifested as ischemic optic neuropathy (ION) and with clinical features of giant cell arteritis (GCA) [14]. The second case was an elderly woman who also developed an ION with no other features of GCA and in whom VZV was demonstrated in the ipsilateral temporal artery; importantly the patient had no history of recent zoster [15]. The third case was a 54-year-old diabetic patient, also with no history of recent zoster, who developed an ION followed by acute retinal necrosis and temporal artery infection [16].

These remarkable reports were followed up by studies aimed at addressing the incidence of VZV infection in

patients with biopsy-negative GCA temporal arteries. Immunohistochemical examination of archived biopsy-negative temporal arteries for the presence of VZV antigen from patients with clinically suspect GCA revealed VZV in 5 of 24 (21%) such temporal arteries [17]. All 5 subjects whose temporal arteries contained VZV antigen presented with clinical and laboratory abnormalities of GCA and early visual disturbances, indicating that multifocal VZV vasculopathy can present with the full spectrum of features seen in GCA.

The continuing search for VZV antigen in GCA-negative temporal arteries revealed abundant VZV antigen as well as VZV DNA in multiple regions (skip areas) of a GCA-negative temporal artery and in skeletal muscle adjacent to the infected temporal artery [18]. Additional pathological analysis of sections adjacent to those containing viral antigen revealed inflammation involving the arterial media and abundant multinucleated giant cells characteristic of GCA [18], thus providing virologic support for the notion that VZV may cause GCA. Currently, both normal extracranial temporal arteries and GCA-positive temporal arteries are under intense scrutiny for the presence of VZV.

Overall, while varicella after primary VZV infection is typically benign, disease after VZV reactivation is often serious, with zoster emerging as an important risk factor for stroke, TIA, and MI. In fact, all of the epidemiologic studies discussed above that reveal an increased risk of stroke after zoster are likely to underestimate the real risk, because VZV frequently reactivates to produce vasculopathy in the absence of zoster rash [19]. Among the more worrisome complications of

VZV vasculopathy is GCA, the most common cause of vasculitis in elderly persons. The growing awareness of the role of VZV in vascular disease promises to lead to clinical trials to assess the benefit of antiviral therapy. The field is moving rapidly.

Notes

Acknowledgments. The authors thank Marina Hoffman for editorial assistance and Lori DePriest for word processing and formatting.

Financial support. This work was supported by the National Institutes of Health (grants AG032958, AG006127, NS067070).

Potential conflicts of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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