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Review article

# Varicella zoster virus vasculopathy: The expanding clinical spectrum and pathogenesis

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ABSTRACT

Varicella zoster virus (VZV) is a ubiquitous, human alphaherpesvirus that produces varicella on primary infection then becomes latent in ganglionic neurons along the entire neuraxis. In elderly and immunocompromised individuals, VZV reactivates and travels along nerve fibers peripherally resulting in zoster. However, VZV can also spread centrally and infect cerebral and extracranial arteries (VZV vasculopathy) to produce transient ischemic attacks, stroke, aneurysm, sinus thrombosis and giant cell arteritis, as well as granulomatous aortitis. The mechanisms of virus-induced pathological vascular remodeling are not fully elucidated; however, recent studies suggest that inflammation and dysregulation of programmed death ligand-1 play a significant role.



**Contents**

1. Introduction . . . 112
2. Epidemiology . . . 113
3. Clinical features, laboratory abnormalities, diagnosis and treatment of VZV vasculopathy . . . 113
4. Giant cell arteritis . . . 114
5. Granulomatous aortitis . . . 114
6. VZV in normal human temporal arteries and intracerebral arteries . . . 115
7. Pathogenesis . . . 115
8. Conclusions . . . 116
Statement of interest . . . 116
Acknowledgments . . . 116
References . . . 116

## 1. Introduction

Varicella zoster virus (VZV) is an exclusively human neurotropic alphaherpesvirus that infects >95% of the U.S. population. Primary infection typically results in varicella (chickenpox), followed by establishment of virus latency in neurons of the cranial nerve, dorsal root and autonomic ganglia along the entire neuraxis, as well as of the adrenal glands (Badani et al., 2016). With a decline in VZV-specific cell-mediated immunity in elderly and immunocompromised individuals, defects in innate immunity (particularly NK cell defects; Levy et al.,

*Abbreviations:* GCA, giant cell arteritis; IL, interleukin; MHC-1, major histocompatibility complex class I; MMP, matrix metalloproteinase; PD-L1, programmed death ligand-1; TA, temporal artery; VZV, varicella zoster virus.

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2003; Orange, 2013) or the presence of anti-cytokine antibodies (Burbelo et al., 2010; Chi et al., 2013), virus reactivates from one of more ganglia, travels peripherally to skin and produces herpes zoster (shingles) in the corresponding dermatome(s). Zoster is frequently complicated by postherpetic neuralgia, which is the leading cause of pain-related suicide in the elderly (Schamder, 1998).

During reactivation, VZV can also travel centrally to produce other neurological and ocular diseases with or without associated zoster rash. One such disease is VZV vasculopathy produced by direct VZV infection of arteries that is associated with inflammation and clinical symptoms and signs. VZV vasculopathy was first described in 1896 (Baudouin and Lantuejoul, 1919) and included cases of varicella or zoster that was temporally associated with stroke, particularly when zoster occurred in the ophthalmic division of the trigeminal nerve (herpes zoster ophthalmicus with contralateral hemiparesis). Subsequently, affected cerebral arteries from patients with VZV vasculopathy were examined postmortem and found to have VZV DNA following DNA extraction from affected arteries and PCR for viral DNA, VZV antigen by immunohistochemical analyses and herpesvirus particles by electron microscopy (Fukumoto et al., 1986; Gilden et al., 1996) demonstrating that VZV vasculopathy was due to productive virus infection of arteries. Over the past few decades, the clinical spectrum of VZV vasculopathy has expanded to include extracranial vasculopathy presenting as giant cell arteritis, the most common systemic vasculitis in the elderly, and granulomatous aortitis. Herein, we will discuss these varied clinical presentations, as well as the pathogenesis of VZV infection of arteries and persistent inflammation contributing to pathological vascular remodeling.

## 2. Epidemiology

VZV infection as a cause of stroke is supported by the clear demonstration that *zoster is a stroke risk factor* in multiple epidemiological studies from Taiwan, Denmark, the U.K., Sweden and the U.S. Two studies using the Taiwan National Health Research Institute records revealed a 30% increased risk of stroke within 1 year following zoster (Kang et al., 2009) and a 4.5-fold increased risk if zoster occurred in the ophthalmic division of the trigeminal nerve (Lin et al., 2010). A study using records from the Danish National Registry indicated that after zoster, there was a 126% increased risk of stroke within 2 weeks, 17% increased risk from 2 weeks to 1 year and 5% increased risk after the first year (Sreenivasan et al., 2013). A study from the UK Health Improvement Network general practice database showed that the risk for transient ischemic attacks (TIAs) and myocardial infarctions (MIs) were increased by 1.15- and 1.10-fold, respectively, in all patients with zoster; however, in patients under 40 years of age with zoster, the risk for stroke, TIAs and MIs was significantly higher (1.74-, 2.42- and 1.49-fold, respectively) (Breuer et al., 2014). A study from the U.K. Clinical Practice Research Datalink showed a decreasing risk of stroke over time after zoster in all dermatomes, with a statistically significant age-adjusted incidence at 1–4 weeks after zoster (1.63), 5–12 weeks after zoster (1.42), and 13–26 weeks after zoster (1.23), but no increase at later times (Langan et al., 2014). In patients with ophthalmic-distribution zoster, the risk of stroke was increased 3-fold at 5 to 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.

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 (Sundström et al., 2015). Like the U.K. study, in patients 39 years and younger, the risk of stroke 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 (Minassian et al., 2015). Finally, in the first U.S. population-based study, the risk of stroke within 3 months of zoster was increased 1.53-fold (Yawn et al., 2016). While stroke in the pediatric population is rare, approximately one-third of arterial ischemic stroke is associated with varicella (Askalan et al., 2001) and 44% of transient cerebral arteriopathy is preceded by varicella (Braun et al., 2009). Overall, these combined studies show that varicella and zoster are risk factors for stroke, particularly in individuals who develop zoster under 40 years of age, consistent with central spread of VZV to arteries in addition to peripheral spread to skin; furthermore, antiviral therapy may decrease this stroke risk and should be considered in all cases of zoster.

## 3. Clinical features, laboratory abnormalities, diagnosis and treatment of VZV vasculopathy

Historically, VZV vasculopathy was initially characterized as involving intracranial arteries and presented as transient ischemic attacks (TIAs) and ischemic or hemorrhagic strokes. In 30 patients with virologically-confirmed VZV vasculopathy (Nagel et al., 2008), rash was present in 63%, cerebrospinal (CSF) pleocytosis was detected in 67% and the average time from rash to neurological symptoms and signs was 4.1 months. Brain MRI and CT abnormalities were present in 97%, typically seen as enhancing lesions at grey-white matter junctions. Of 23 patients analyzed by angiography, 70% had abnormalities predominantly in both large and small arteries (50%), small arteries exclusively (37%), and large arteries exclusively (13%). Due to the protracted nature of disease, VZV DNA was detected in only 30% of CSF samples whereas anti-VZV IgG antibody was found in 93% of CSF samples, including a reduced serum/CSF ratio of anti-VZV IgG that confirmed intrathecal synthesis of anti-VZV IgG (Nagel et al., 2007, 2008). While both PCR and detection of antibody to VZV in CSF are highly specific, detection of anti-VZV IgG antibody in CSF is the more reliable test to diagnose VZV vasculopathy (Nagel et al., 2007). Overall, a positive PCR for VZV DNA in CSF can be diagnostic, but a negative PCR does not exclude the diagnosis; only negative results in both VZV PCR and anti-VZV IgG antibody testing in CSF excludes the diagnosis of VZV vasculopathy. Unfortunately, the diagnosis of VZV vasculopathy is often missed, and hence antiviral treatment not administered, due to the lengthy time between the occurrence of rash to stroke, the absence of rash or the absence of a pleocytosis and VZV DNA in CSF.

In children, post-varicella stroke is usually monophasic (Lanthier et al., 2005), typically presenting as an acute hemiparesis at, on average, 4 months after varicella (Ciccone et al., 2010; Miravet et al., 2007). Recently, the live attenuated varicella vaccine strain was shown to cause VZV vasculopathy in an immunodeficient child (Sabry et al., 2014), indicating the need for caution in vaccinating potentially immunocompromised children.

Less commonly, VZV vasculopathy can present as aneurysms with subarachnoid hemorrhage. A classic case describes a 41-year-old woman with systemic lupus erythematosus treated with methotrexate (Liberman et al., 2014), who developed zoster in multiple dermatomes and severe headache; 2 months later, subsequent 4-vessel digital subtraction angiography revealed 9 anterior circulation aneurysms. Treatment with intravenous acyclovir resulted in resolution of symptoms, reduction in the size of most aneurysms and complete resolution of the 2 largest aneurysms. Rarely, VZV vasculopathy may also present as acute venous sinus thrombosis (Siddiqi et al., 2012). In a classic case, a 30-year-old man developed varicella followed 1 week later by neurological deficits; MR venography demonstrated a transverse and sigmoid sinus thrombosis. In 2 other cases, patients presented with zoster followed by seizures and extensive cerebral venous sinus thrombosis on neuroimaging.

VZV vasculopathy should be suspected in individuals, particularly if immunocompromised, who have had a stroke or aneurysm with: (1) a recent history of varicella or zoster, (2) recurrence of unclear cause with or without rash, or (3) unclear etiology and absence of stroke risk factors. The best test for diagnosis in these suspected cases is a lumbar puncture and examination of CSF for the presence of anti-VZV