The challenging patient with varicella-zoster virus disease

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Summary

Varicella-zoster virus (VZV) reactivation from latently infected ganglia causes multiple neurologic diseases. The most common is herpes zoster, which is frequently complicated by postherpetic neuralgia, meningoencephalitis, and vasculopathy, including VZV temporal arteritis, myelopathy, and retinal necrosis. All of these disorders can develop without rash. Importantly, VZV vasculopathy is emerging as a significant cause of TIAs and stroke. In particular, a subset of patients who present with symptoms and signs of giant cell arteritis (GCA), but whose temporal artery biopsies are GCA-negative, have multifocal VZV vasculopathy with temporal artery infection. Herein we focus on the specific diagnostic and therapeutic challenges that clinical neurologists encounter in diseases caused by VZV, discuss guidelines for zoster vaccine, and highlight molecular features of VZV latency with a focus on preventing the serious neurologic and ocular complications of VZV reactivation.

Varicella-zoster virus (VZV) is an exclusively human, ubiquitous neurotropic α -herpesvirus. Primary infection usually causes varicella (chickenpox), after which virus become latent in ganglionic neurons along the entire neuraxis.

With age or immunosuppression, cell-mediated immunity to VZV declines, leading to virus reactivation that manifests as zoster (shingles). Zoster is characterized by dermatomal distribution pain and rash (figure 1) and is frequently complicated by chronic pain (postherpetic neuralgia [PHN]) as well as meningoencephalitis, myelopathy, retinal necrosis, and vasculopathy, including multifocal VZV vasculopathy with temporal artery infection (figure 2). A major diagnostic challenge to the practicing neurologist is that all of these disorders can occur without rash, as well as months after rash, and frequently in the absence of a CSF pleocytosis or amplifiable VZV DNA

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Figure 1 Characteristic varicella-zoster virus and herpes simplex virus-1 rash

Varicella-zoster virus reactivation is manifest by dermatomal skin lesions (left), while herpes simplex virus reactivation is manifest by mucosal or patchy skin lesions (right). Both are vesicular on an erythematous base.

in CSF. In fact, detection of anti-VZV antibody in the CSF is often superior to detection of VZV DNA in CSF to diagnose the multiple neurologic complications that follow VZV reactivation without rash¹; thus both tests should be performed in the evaluation of patients with neurologic disease that might be produced by VZV. Furthermore, treatment is often challenging, not only to

Figure 2 With a decline in varicella-zoster virus-specific cell-mediated immunity, virus reactivates from ganglionic neurons and spreads peripherally or centrally to cause disease

Peripheral spread to the skin causes herpes zoster. Central spread to the brain causes meningoencephalitis, while central spread to intracranial and extracranial arteries produces vasculopathy and varicella-zoster virus temporal arteritis, respectively. Central spread to the spinal cord causes myelopathy, while spread to spinal cord arteries causes spinal cord infarction.

Table Features of neurologic diseases produced by varicella-zoster virus

Disease	Clinical features	Imaging	Diagnosis	Treatment
Herpes zoster	Pain and rash	MRI may reveal enhancement of affected ganglia	Unilateral, dermatomal distribution vesicular rash	Valacyclovir 1 g TID × 7 d
Postherpetic neuralgia	Persistent, unilateral, dermatomal distribution pain >3 months after zoster	Not applicable	Chronic, unilateral, dermatomal distribution pain >3 months after zoster	First-line: TCA, gabapentin, pregabalin, lidocaine patch Second- and third-line: opioids, tramadol, 5% lidocaine patch, capsaicin cream, or 8% capsaicin patch
Meningoencephalitis^a	Headache, cognitive changes, focal neurologic symptoms/signs	MRI may reveal meningeal enhancement	CSF: anti-VZV IgG and IgM; PCR: VZV DNA; serum: anti-VZV IgM	Acyclovir, IV 10–15 mg/kg TID × 10–14 days
Myelopathy^a	Progressive paraparesis, incontinence; may recur	MRI: serpiginous lesion or infarction in spinal cord	CSF: anti-VZV IgG and IgM; PCR: VZV DNA; serum: anti-VZV IgM	Acyclovir, IV 10–15 mg/kg TID × 10–14 days
Vasculopathy^a	Headache, cognitive changes, focal neurologic symptoms/signs	MRI: lesions at gray-white matter junction, deep-seated > superficial MRA: focal stenosis	CSF: anti-VZV IgG and IgM; PCR: VZV DNA; serum: anti-VZV IgM	Acyclovir, IV 10–15 mg/kg TID × 10–14 days
VZV multifocal vasculopathy with temporal artery infection^a	Loss of vision, periorbital pain, headache	MRA may reveal ophthalmic artery occlusion	CSF: anti-VZV IgG and IgM; PCR: VZV DNA; serum: anti-VZV IgM; consider temporal artery biopsy to detect VZV antigen	Acyclovir, IV 10–15 mg/kg TID × 10–14 days
Zoster sine herpete	Chronic unilateral, dermatomal distribution pain without rash		CSF: anti-VZV IgG and IgM; PCR: VZV DNA; serum: anti-VZV IgM	Acyclovir, IV 10–15 mg/kg TID × 10–14 days
Abbreviations: Ig = immunoglobulin; MRA = magnetic resonance angiography; TCA = tricyclic antidepressant; VZV = varicella-zoster virus.				
^a Can occur without rash.				

relieve the pain of PHN, but also to manage VZV vasculopathy and myelopathy, which may be recurrent and protracted. The table lists the clinical features, imaging abnormalities, and laboratory tests needed for virologic confirmation and treatment of neurologic diseases produced by VZV reactivation.

Postherpetic neuralgia

PHN is operationally defined as dermatomal-distribution pain that persists for more than 3 months after zoster. Age is the most important risk factor. More than 30% of zoster patients >60 years of age develop PHN. PHN is also slightly more frequent in women and after trigeminal-distribution zoster.² PHN may be due to a chronic ganglionitis from persistent viral infection. Chronic inflammatory cells were found in ganglia from patients with PHN of 2.5 months³ and 2 years⁴ duration; furthermore, VZV DNA and proteins were found in

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blood mononuclear cells of many patients with PHN.^{5,6} Although treatment of acute zoster with corticosteroids does not prevent PHN, some patients improved with intense antiviral treatment.⁷ Currently, treatment of PHN with IV acyclovir is not Food and Drug Administration (FDA)–approved. Further well-designed, randomized controlled trials of antiviral agents with more participants are needed. Management of PHN is challenging, particularly in elderly patients. The table provides recommendations for first-, second-, and third-line therapy. Combination therapy such as gabapentin and nortriptyline, morphine and gabapentin, or pregabalin with a lidocaine 5% patch may provide greater analgesic effects. Lower starting doses and slower titrations to therapeutic dose in elderly patients must be used.

A newer potentially promising treatment is percutaneous peripheral nerve field stimulation. Under monitored anesthesia care, stimulating electrodes are placed subcutaneously over the area of maximal pain. Leads are connected to an external pulse generator for 2–14 days. If there is >50% improvement of pain, a permanent pulse generator is implanted. This can be done in an outpatient setting. Many subjects became pain-free with minimal to no medication needed after ophthalmic-, cervical-,⁸ and thoracic-distribution PHN.

VZV vasculopathy

Productive VZV infection of cerebral arteries causes ischemic and hemorrhagic stroke (VZV vasculopathy). VZV vasculopathy is not uncommon, given that herpes zoster affects >50% of individuals by 80 years of age and increases the risk of stroke by 30% within the following year and by 4.5-fold if zoster is in the ophthalmic distribution of the trigeminal nerve.⁹ Recognition, diagnosis, and treatment of VZV vasculopathy pose a significant challenge.

VZV vasculopathy should be suspected in a patient with a recent history of herpes zoster or varicella who presents with a TIA, stroke, or altered mental status, and should also be considered in patients with a stroke of unknown origin, particularly among immunocompromised and HIV-seropositive patients. The absence of a history of rash or a CSF pleocytosis should not deter the clinician from pursuing a diagnostic evaluation for VZV vasculopathy since one-third of patients have no preceding rash or a CSF pleocytosis.¹

Supportive data include a mononuclear pleocytosis in CSF and MRI findings consistent with an ischemic or hemorrhagic lesion, particularly at gray–white matter junctions (figure 3A). Large and small arteries are involved in 50%, small arteries in 37%, and large arteries in 13%. Suspicion for VZV vasculopathy as the etiology of stroke is increased in the setting of multifocal or bilateral strokes, particularly when they accrue over days to weeks, and when angiography reveals focal narrowing and beading. Detection of VZV DNA by PCR in CSF is usually positive within the first week after reactivation, after which anti-VZV immunoglobulin G (IgG) antibody is produced. Because VZV vasculopathy is often chronic and protracted, detection of anti-VZV IgG antibody is the best diagnostic test.¹ Overall, CSF of 30% of patients with VZV vasculopathy contained VZV DNA while 93% had anti-VZV IgG antibody.¹ We recently encountered a case that produced 5 strokes over a 2-year period, was verified by anti-VZV antibody in CSF, yet still had a favorable outcome after treatment.¹⁰

Finally, immunocompetent patients with VZV vasculopathy should be treated with a full 14-day course of IV acyclovir, 10–15 mg/kg given 3 times daily. Immunocompromised patients or those with recurrent VZV vasculopathy may need a longer course. Since virus-infected arteries

Figure 3 Varicella-zoster virus vasculopathy and myelopathy on MRI

(A) Varicella-zoster virus (VZV) vasculopathy is characterized by deep-seated lesions, typically at gray-white matter junctions (arrows). (B) VZV myelopathy is characterized by longitudinal serpiginous lesions in the spinal cord (arrow).

typically contain inflammatory cells, we give oral prednisone, 1 mg/kg daily for 5 days without taper. Patients with renal disease must be monitored closely when treated with IV acyclovir.

Multifocal VZV vasculopathy with temporal artery infection

Multifocal VZV vasculopathy with temporal artery infection is emerging as an important clinical disorder after VZV reactivation. VZV temporal arteritis and giant cell arteritis (GCA) both manifest with headache, with or without loss of vision, an elevated sedimentation rate (ESR), and increased C-reactive protein (CRP). Recently, we encountered 2 elderly patients with clinical and laboratory features of GCA in whom temporal artery (TA) biopsy was negative for GCA. The first patient was an 80-year-old man with left ophthalmic-distribution zoster who developed painless ipsilateral loss of vision with elevated ESR and CRP, was diagnosed clinically with possible GCA, and treated with steroids without improvement of vision. TA biopsy was GCA-negative, but analysis revealed inflammation and VZV antigen in the adventitia, after which he was treated with IV acyclovir and vision improved.¹¹ A second even more remarkable patient was a 75-year-old woman without a history of zoster, who developed left periorbital pain and loss of vision with elevated ESR and normal CRP; she was treated with steroids for presumed GCA and vision worsened. TA biopsy revealed inflammation and VZV antigen in the adventitia, and CSF analysis revealed the presence of anti-VZV IgG antibody with reduced serum/CSF ratios of anti-VZV IgG antibody compared to ratios for albumin and total IgG, indicative of intrathecal synthesis of anti-VZV IgG antibody; vision improved after antiviral treatment.¹² Overall, we have learned that in some patients who manifest clinically as GCA but whose TAs are GCA-negative, VZV infected their extracranial temporal arteries and produced temporal arteritis. In both patients (with and without zoster), treatment with steroids for presumed GCA resulted in no improvement or actual worsening of vision, VZV antigen was present in TA biopsies, and antiviral treatment improved vision. While the frequency of VZV temporal arteritis among patients with acute onset unilateral headache and visual loss, elevated ESR and CRP, and pathologically GCA-negative temporal artery biopsies is unknown, this diagnosis must be considered if such patients worsen or do not improve with steroids. TA biopsies should be examined for VZV antigen, and if positive, these patients should be treated with IV acyclovir.

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VZV myelopathy

VZV can spread centrally to the spinal cord to cause myelitis from frank invasion of virus or to produce spinal cord infarction. Patients present with paraparesis with or without sensory features and often without rash. MRI of the spinal cord reveals longitudinal, serpiginous enhancing lesions in myelitis (figure 3B) and diffusion-weighted abnormalities after spinal cord infarction. CSF contains antibodies to VZV indicative of intrathecal synthesis, and treatment is with IV acyclovir.

Zoster sine herpete

Zoster sine herpete is defined as chronic radicular pain without rash caused by VZV. It was initially described in patients with dermatomal distribution radicular pain in areas distinct from pain with zoster rash.¹³ Virologic verification of zoster sine herpete was first provided by detection of VZV DNA in CSF¹⁴ or in blood mononuclear cells, as well as by detection of anti-VZV IgG antibody in CSF and a favorable response to antiviral therapy in patients with chronic radicular pain. The most compelling evidence that persistent radicular pain without rash is caused by chronic active VZV ganglionitis came from analysis of a trigeminal ganglionic mass removed from an immunocompetent adult who had experienced persistent trigeminal-distribution pain for more than a year; pathologic and virologic analyses of the ganglionic mass revealed active VZV ganglionitis, and the patient responded well after surgical removal of the infected mass and antiviral therapy.¹⁵ The recognition and diagnosis of zoster sine herpete is challenging. When a patient presents with unilateral dermatomal distribution pain without rash, diabetic radiculopathy or nerve impingement must be ruled out by imaging. If zoster sine herpete is confirmed virologically, patients should be treated with IV acyclovir, 10–15 mg/kg for 10–14 days.

Retinal necrosis VZV infection produces acute retinal necrosis (ARN) or progressive outer retinal necrosis. ARN presents with periorbital pain and floaters with hazy vision and loss of peripheral vision. Progressive outer retinal necrosis presents with painless loss of vision, floaters, and constricted visual fields with resultant retinal detachment. Multifocal, discrete opacified lesions begin in the outer retinal layers peripherally or posterior pole; only late in disease are inner retinal layers involved. Diffuse retinal hemorrhages and whitening with macular involvement bilaterally are characteristic findings. VZV is the most common cause of progressive outer retinal necrosis, although HSV and cytomegalovirus can also cause this disease. Most cases are seen in patients with AIDS with CD4+ T-cell counts less than 10 cells/mm³ of blood. Treatment is typically IV acyclovir, steroids, and aspirin followed by oral acyclovir. Intravitreal injections of foscarnet and oral acyclovir have also been effective. The best treatment for progressive outer retinal necrosis in patients with AIDS may be prevention with highly active antiretroviral therapy.

Zostavax immunization In 2006, a VZV vaccine (Zostavax, Merck) that boosts cell-mediated immunity to VZV was approved by the FDA for immunocompetent individuals over age 60 years with no recent history of zoster. Zoster vaccine is safe and effective. When administered to people in this age group, Zostavax boosted VZV-specific T-cell-mediated immunity (CD4 and CD8 cells, CD4 and CD8 effector memory T cells, and CD8 early-effector T cells), with a half-life of the

boost of at least 5 years.¹⁶ Clinically, the 3-year Shingles Prevention Study showed that Zostavax significantly reduced burden of disease due to zoster and PHN.¹⁷ Zostavax is given once after age 60. No booster dose is recommended. Despite its cost-effectiveness for adults ages 65–75 years as determined in the United States, Canada, and United Kingdom, Zostavax vaccination among eligible adults aged 60 and older has increased only slowly in the United States, from 1.9% during 2007 (the year after licensure) to 14.4% in 2010 (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6104a2.htm>). There are several reasons for this slow uptake, including the high cost of the vaccine, its freezer requirement, and complicated insurance coverage. Perhaps most importantly, vaccine supply has been repeatedly disrupted, which has reduced provider and patient interest as well as promotional efforts. Merck vaccine is now widely available, and the “shingles vaccine” is being widely advertised. Disparities in uptake based on race and ethnicity have also been noted.

Latency and current basic research

Unlike type 1 herpes simplex virus (HSV), which reactivates from latency in cranial nerve ganglia to produce mucosal lesions around the mouth and nose, and unlike type 2 HSV, which is latent in sacral ganglia and reactivates to produce genital herpes, VZV is latent in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis; thus, zoster can occur anywhere on the body. VZV is latent in more than 90% of people. In human ganglia latently infected with VZV, the entire virus genome is present in a circular configuration. VZV DNA is extrachromosomal but is associated with cellular histone complexes that function, in part, to regulate virus gene transcription. The abundance of VZV is highly variable. During latency, at least 12 VZV gene transcripts have been detected,^{18,19} although the latest state-of-the-art technology of multiplex reverse transcriptase PCR revealed no VZV transcripts at a postmortem interval of 9 hours or less.²⁰ Considerable VZV research continues to focus on understanding the configuration of viral DNA and extent of viral gene expression in latently infected human ganglia with an eye toward preventing viral reactivation.

Challenges

VZV reactivation leads to herpes zoster, which is frequently complicated by PHN as well as meningoencephalitis, myelopathy, retinal necrosis, and vasculopathy, including VZV temporal arteritis. Thus, patients who present with these conditions should be queried for a history of zoster within the past year, since many of the neurologic conditions develop months after zoster. Furthermore, even without rash, VZV should be considered as a possible etiologic agent. For diagnosis of VZV-induced CNS disease, the CSF should be examined for both VZV DNA and anti-VZV antibody; in VZV vasculopathy and myelopathy, which are often protracted, detection of anti-VZV antibody is often more sensitive than PCR for VZV DNA. For treatment of PHN, caution must be used in elderly patients, with medications started at lower doses and titrated slowly; immunocompromised patients or those with recurrent CNS disease need to be treated >14 days with IV acyclovir. Finally, immunocompetent individuals over age 60 years with no history of recent zoster should be immunized with Zostavax.

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