

Stroke caused by varicella zoster virus

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**INTRODUCTION** — Varicella zoster virus (VZV) infection of cerebral arteries produces a vasculopathy, manifesting most often as ischemic stroke and less often as hemorrhagic stroke. Vasculopathy can occur after either primary infection with VZV (ie, varicella; chickenpox) or after viral reactivation (ie, herpes zoster; shingles) [1].

This topic will review the pathogenesis, epidemiology, risk factors for, clinical features, diagnosis, and treatment of VZV vasculopathy. The major clinical manifestations and complications of chickenpox and herpes zoster are discussed separately. (See "[Epidemiology of varicella-zoster virus infection: Chickenpox](#)" and "[Treatment of varicella-zoster virus infection: Chickenpox](#)" and "[Vaccination for the prevention of varicella-zoster virus infection: Chickenpox](#)" and "[Clinical manifestations of varicella-zoster virus infection: Herpes zoster](#)" and "[Prevention of varicella-zoster virus infection: Herpes zoster](#)".)

**GENERAL BACKGROUND** — VZV vasculopathy has previously been called granulomatous angiitis, VZV vasculitis, or post-varicella arteriopathy; a subset of patients have specific ocular and motor findings known as herpes zoster ophthalmicus with delayed contralateral hemiparesis.

Early reports described ischemic large vessel strokes, although it is now appreciated that both large and small arteries are commonly involved. An expanded spectrum of stroke caused by VZV infection has been increasingly recognized including aneurysm, subarachnoid and intracerebral hemorrhage, arterial ectasia, and possibly dissection [2-4].

**VIROLOGY** — VZV is a ubiquitous human DNA virus of the herpesvirus family. Primary infection occurs via respiratory aerosols or contact with vesicles from an infected individual and results in the characteristic, disseminated rash of varicella (ie, chickenpox).

After primary infection, VZV becomes latent within neurons in cranial nerve, dorsal root, and autonomic ganglia along the entire neuraxis [5]. A decline in virus-specific cell-mediated immunity to VZV in elderly and immunocompromised individuals results in virus reactivation in one or more ganglia. VZV reactivation most commonly manifests as herpes zoster (ie, shingles), which may be complicated by postherpetic neuralgia.

Less often, VZV reactivation leads to other neurologic and ocular complications, such as retinal necrosis [6], myelopathy [7], and VZV vasculopathy [8]. Any of these complications of VZV infection can occur without the characteristic rash of zoster. (See "[Clinical manifestations of](#)

[varicella-zoster virus infection: Herpes zoster](#)" and "[Epidemiology and pathogenesis of varicella-zoster virus infection: Herpes zoster](#)".)

## PATHOGENESIS

Direct infection of blood vessels by VZV — The likely mechanism by which VZV causes stroke is by direct infection of cerebral arteries, which leads to a spectrum of both inflammatory and noninflammatory pathological changes including thrombosis, necrosis, dissection, and aneurysm formation [9]. Various animal studies have identified afferent fibers from trigeminal and dorsal root ganglia to both intracranial and extracranial blood vessels, thus providing an anatomic pathway for transaxonal spread of virus [10-12].

Pathology — In autopsy studies of patients who died of VZV vasculopathy, pathological and virological analyses have revealed herpes virions [13,14], VZV DNA, VZV antigen, and multinucleated giant cells [15-21] within the walls of cerebral arteries ([picture 1](#)).

Role of autoantibodies — A potential role for autoantibodies to phospholipids and coagulation proteins during or after varicella has been suggested, although the contribution of these transient autoantibodies in the occlusion of cerebral arteries is unclear [22,23]. One report described an adult with varicella who developed a stroke and multiple peripheral thrombotic events associated with a transient protein S deficiency and transient anticardiolipin and anti-beta 2 glycoprotein antibodies [24]. The presence of lupus anticoagulant [25], protein S deficiency [25,26], and anti-protein S antibody [26] in association with varicella infection has also been described.

## EPIDEMIOLOGY

Children — Varicella is an important risk factor for childhood arterial ischemic stroke [27]. Approximately 1 in 15,000 cases of varicella infection is associated with subsequent stroke [27]; most of these events occur within 12 months of prior varicella infection [28]. Furthermore, varicella infection precedes the onset of stroke in 44 percent of cases of transient cerebral arteriopathy of childhood [29]. Within a large international study of immunocompetent children presenting with stroke, 277 (53 percent) had an arteriopathy, including 19 children (7 percent) with a history of varicella-associated stroke [28]. (See '[Risk factors](#)' below and "[Ischemic stroke in children and young adults: Etiology and clinical features](#)".)

Adults — In adults, VZV vasculopathy is reported more commonly in immunocompromised than in immunocompetent individuals. Prior to the introduction of potent antiretroviral therapy, CNS infection caused by VZV was detected in 1.5 to 4.4 percent of autopsy cases among HIV-infected patients with documented vasculopathy [16,17,30] and leukoencephalitis [17,30-32]; most of these cases occurred in patients with severe CD4 T-cell depletion. VZV vasculopathy has also been rarely reported among renal transplant recipients [33].

## RISK FACTORS

Varicella infection — Risk factors for stroke caused by VZV include a history of varicella within the past 12 months [27-29]. Using a health care database in Taiwan, a study was performed to

evaluate the risk of stroke within one year following an episode of herpes zoster among 7760 cases compared with 23,280 controls [34]. After adjusting for other cardiovascular risk factors, the adjusted hazards ratio of risk of stroke among persons 45 years or older with a history of herpes zoster was 1.31 (95% CI, 1.06-1.63) compared with controls. The incidence of stroke following herpes zoster ophthalmicus was higher than among those patients with a history of herpes zoster at other cutaneous locations (1.7 versus 5.8 percent) [34].

Immunosuppression — VZV-associated stroke has been described in patients with advanced HIV infection, sometimes accompanied by acute retinal necrosis [35,36]. Cases have also occurred in immunocompromised patients with leukemia, lymphoma, and among those taking immunosuppressive therapies for systemic lupus erythematosus and rheumatoid arthritis [8].

## CLINICAL MANIFESTATIONS

Neurologic manifestations — The classic clinical presentation of VZV vasculopathy in adults is ophthalmic distribution zoster followed by acute contralateral hemiplegia; or in children, varicella followed by onset of acute hemiplegia. However, since VZV may affect both large and/or small arteries resulting in cerebral ischemia or hemorrhage, clinical presentations vary widely and include headache, mental status changes, aphasia, ataxia, hemisensory loss, and both hemianopia or monocular visual loss [37,38]. Some patients may also present with symptoms and signs consistent with encephalitis (eg, mental status changes) followed by a focal deficit [19].

Less frequently, patients with VZV vasculopathy present with a transient ischemic attack, aneurysm, subarachnoid or cerebral hemorrhage, carotid dissection, and, rarely, peripheral arterial disease [1,4].

Rash — Approximately two-thirds of patients have a history of zoster or varicella rash [8]. The average time from rash to neurologic symptoms and signs is 4.1 months among those who have a history of zoster [8]; on occasion the patient can present with rash and stroke simultaneously. Since both zoster and stroke occur mostly in people over age 60, clinicians might not consider VZV vasculopathy as a cause of transient ischemic attacks or stroke months after presenting with herpes zoster.

It is important for clinicians to be aware that approximately one-third of patients have no history of rash; thus, the absence of rash should not dissuade clinicians from pursuing a diagnostic workup for VZV in the appropriate clinical setting.

Other complications — VZV vasculopathy may also coexist with other neurologic complications such as VZV meningitis, radiculitis, cranial nerve disease, and myelitis or spinal cord infarction [39].

IMAGING — All patients presenting with a stroke should have imaging studies. The relative advantages of the various imaging modalities are discussed elsewhere. (See "[Neuroimaging of acute ischemic stroke](#)" and "[Overview of the evaluation of stroke](#)" and "[Initial assessment and](#)

[management of acute stroke](#)" and "[Ischemic stroke in children: Evaluation, initial management, and prognosis](#)".)

Brain imaging — VZV vasculopathy involves both large and small arteries. Brain imaging shows ischemic or hemorrhagic infarction in virtually all cases of virologically confirmed VZV vasculopathy [8]. MRI typically demonstrates both superficial and deep-seated lesions, in both gray and white matter, and particularly at gray-white matter junctions ([image 1](#)), a clue to the cause of disease. Most lesions are bland, but hemorrhagic lesions also occur; some lesions enhance. Whereas multifocal lesions are common and thus give a clue to diagnosis, VZV vasculopathy also produces single lesions; in early reports, a single large infarct seen in the same location as the cutaneous rash was referred to as "herpes zoster ophthalmicus with contralateral hemiparesis".

Although gray-white matter lesions are often seen in patients with other disorders, such as metastatic carcinoma and embolic disease, VZV vasculopathy should be included in the differential diagnosis of patients with gray-white matter junction lesions.

Angiographic features — Ischemic or hemorrhagic infarction at gray-white matter junctions should prompt consideration of vascular studies, such as magnetic resonance arteriogram, CT angiography or conventional contrast dye angiography in conjunction with virological testing. Typical angiographic changes produced by VZV include segmental constriction, often with poststenotic dilatation ([image 1](#)). These features can also be seen in patients with other CNS vasculitides. (See "[Primary angiitis of the central nervous system](#)".)

In addition to arterial occlusion, aneurysm and hemorrhage are also seen. In the largest series of 30 patients with virologically verified VZV vasculopathy, 23 patients underwent vascular studies (conventional angiography or MRA) and 16 (70 percent) had vascular abnormalities [8]. Brain imaging and vascular studies demonstrated mixed large and small artery involvement in 15, pure small artery involvement in 11, and pure large artery disease in 4 patients. In one report of 25 patients with a variety of infectious vasculopathies, MRI showed enhancement of the arterial wall in two patients with VZV-related disease [40].

While the presence of stenosis or occlusion is helpful in diagnosing VZV vasculopathy, a negative angiogram does not exclude the diagnosis, most likely because disease in small arteries is not detected as readily as in large arteries. Overall, mixed large and small artery disease is seen more often than pure small artery disease, whereas pure large artery disease occurs least often.

**CEREBROSPINAL FLUID TESTING** — Cerebrospinal fluid (CSF) abnormalities are common in patients with VZV vasculopathy. A modest pleocytosis, usually fewer than 100 cells/mm<sup>3</sup>, predominantly mononuclear cells, is seen in approximately two-thirds of patients with VZV vasculopathy [8]. Many patients also have red blood cells in their CSF. CSF protein is usually elevated while glucose is normal. Oligoclonal bands are frequently present [41].

CSF analysis should also include testing for VZV antibodies and VZV DNA. (See "[Diagnosis](#)" below.)

**DIAGNOSIS** — VZV vasculopathy should be suspected in a patient with a recent history of herpes zoster or varicella who presents with a transient ischemic attack, stroke, or altered mental status. VZV vasculopathy should also be considered in patients with a stroke of unknown origin [42], particularly among immunocompromised and HIV-seropositive patients. The absence of a history of rash should not deter the clinician from pursuing a diagnostic evaluation for VZV vasculopathy.

Supportive data include:

- A mononuclear pleocytosis in CSF
- MRI findings consistent with an ischemic or hemorrhagic lesion, particularly at gray-white matter junctions. Suspicion for VZV vasculopathy as the etiology of stroke is increased in the setting of multifocal and/or bilateral strokes, particularly when they accrue over days to weeks.
- Focal narrowing and beading in cerebral vessels on angiography.

The confirmatory laboratory diagnosis is made by demonstrating either the intrathecal production of anti-VZV antibodies or the presence of VZV DNA in the CSF. (See ['Treatment'](#) below.)

**Laboratory testing** — When a clinical diagnosis of VZV vasculopathy is suspected and supported by single or multiple lesions on MRI or CT, further diagnostic testing should be pursued with testing for both anti-VZV IgG and for VZV DNA (by quantitative polymerase chain reaction assay) in CSF. The assay uses primers specific for VZV, sensitive enough to detect approximately 100 copies of viral DNA.

Testing for anti-VZV IgG antibody in the CSF generally has a higher yield than testing for VZV DNA; this may be related to late testing in initially unsuspected cases of VZV vasculopathy. For example, in one case report, serial CSF analysis revealed the presence of VZV DNA only during the first two weeks of disease, while anti-VZV IgG antibody subsequently became detectable during the second week after infection [8]. The yield of VZV DNA testing may be higher in immunosuppressed hosts [8].

In the largest series of virologically verified VZV vasculopathy from multiple institutions in the United States, Europe and Japan, 28 of 30 (93 percent) patients with VZV vasculopathy had anti-VZV IgG in the CSF compared with only 30 percent with VZV DNA in CSF; in each of the patients with detectable anti-VZV IgG in CSF, a reduced serum/CSF ratio of VZV IgG confirmed intrathecal synthesis [8]. Quantification of virus-specific IgG in the CSF is frequently performed by calculation of a virus-specific antibody index [43].

The specificity of the enzyme immunoassay test used for detection of VZV antibody appears robust; this test was performed on more than 1600 CSF samples from control subjects with migraine, epilepsy, and other CNS encephalidites (HSV, EBV, West Nile virus); no patient with an alternative diagnosis had detectable anti-VZV IgG antibody [44].

Although a positive PCR for VZV DNA in CSF is diagnostic, a negative PCR does not exclude the diagnosis; only negative results in both VZV PCR and anti-VZV IgG antibody testing in the CSF would exclude the diagnosis of VZV vasculopathy [44].

**DIFFERENTIAL DIAGNOSIS** — VZV is the only human virus that has been shown to replicate in arteries and produce vasculopathy [1]. However, many of the same symptoms, signs, CSF abnormalities (eg, pleocytosis), imaging, and arteriographic abnormalities that occur in VZV vasculopathy are seen in other CNS disorders, such as primary angiitis of the nervous system and granulomatous angiitides of the CNS (eg, sarcoidosis, neurosyphilis, and tuberculous and fungal infections). Thus, the workup of all patients with granulomatous or other CNS angiitides should include CSF analysis for both VZV DNA and anti-VZV IgG antibody.

Hypercoagulable states, multifocal cardiac embolism, and intravascular lymphoma can also produce a pattern of multifocal stroke similar to that seen in vasculitis. (See "[Ischemic stroke in children and young adults: Etiology and clinical features](#)", section on 'Vasculitis'.)

**TREATMENT** — VZV vasculopathy is caused by productive viral infection in arteries, as evidenced by the presence of multinucleated giant cells, herpesvirus particles, VZV DNA, and VZV antigen in cerebral arteries [19]. Prompt treatment in suspected cases of VZV vasculopathy is important to minimize morbidity and mortality.

Because VZV vasculopathy is uncommon, there are no controlled treatment trials to assess the optimal treatment strategies. Patients are typically treated with high-dose [acyclovir](#) intravenously based on the clinical experience of experts, descriptive case series, and recommendations from expert guideline committees.

The largest case series consisted of 30 patients who were treated with antiviral therapy, steroids, or both [8]. In those treated with [acyclovir](#) alone, 66 percent had neurological deficits that improved or stabilized, compared with 75 percent who improved or stabilized when treated with both acyclovir and steroids [8]. Because patients received varying treatment regimens at different institutions in an uncontrolled setting, the determination of the optimal dose, duration of antiviral treatment, and benefit of concurrent steroid therapy awaits prospective studies with larger case numbers.

When the diagnosis of VZV vasculopathy is being considered, and the clinician is awaiting CSF studies that detect anti-VZV IgG antibody or VZV DNA in CSF to confirm the diagnosis, it is advisable to begin treatment immediately with intravenous [acyclovir](#) (10 to 15 mg/kg three times daily). The duration of treatment will depend on the patient's clinical response. (See "[Duration of treatment](#)" below.)

As of November 2012, there is a shortage of IV [acyclovir](#) in the United States due to a manufacturing delay [45,46]. Clinicians should check the [US Food and Drug Administration's website](#) for information about the availability of IV acyclovir. If IV acyclovir is not available, an alternative regimen can be used. Specific recommendations are presented separately. (See "[Acyclovir: An overview](#)", section on 'Acyclovir shortage'.)

Since histologic specimens often demonstrate an inflammatory response in infected cerebral arteries, we give oral [prednisone](#) (1 mg/kg daily for five days) without a steroid taper [9].

**PATIENT MONITORING DURING THERAPY** — During intravenous antiviral therapy, the patient is monitored clinically for stabilization of neurological deficits and observed for the development of any new strokes. Based on our clinical experience, we repeat CSF analysis if:

- The patient is not responding clinically within two weeks of intravenous antiviral therapy
- New lesions appear on MRI

CSF analysis should also include evaluation for other concomitant infectious agents, such as mycobacteria, fungi, and *Treponema pallidum* (the causative agent of neurosyphilis), particularly in the patient with advanced AIDS where multiple infections may coexist. Consultation with an expert in HIV treatment and management is also important regarding the role of antiretroviral therapy.

If the initial CSF contained more than 50 white blood cells/mm<sup>3</sup> and the patient has not returned to baseline, we also repeat CSF examination to see if the pleocytosis is resolving with antiviral therapy.

**DURATION OF TREATMENT** — Initially, we treat patients for a minimum of 14 days with antiviral therapy. If the patient does not improve clinically, or develops new lesions by MRI, or has a persistent pleocytosis, we often treat for an additional two to four weeks with intravenous [acyclovir](#) based on our clinical experience.

Unlike most acute viral encephalitides, VZV vasculopathy is often chronic and protracted. We have encountered multiple patients with VZV vasculopathy who continue to have new neurologic symptoms such as focal weakness and altered mental status after intravenous [acyclovir](#) treatment. Most patients were HIV-seropositive or had AIDS; one patient had diabetes.

**PREVENTION** — Studies suggest that the risk of stroke is increased for at least one year after herpes zoster [34]. Thus, it is plausible that widespread use of [zoster vaccine](#) may decrease the risk of VZV vasculopathy, since immunization generates an increase in VZV-specific cell-mediated immunity [47]. One retrospective study demonstrated that [herpes zoster vaccine](#) was effective in reducing herpes zoster disease and VZV-related hospitalizations for complications among persons between 60 and 80 years of age [48]. (See "[Prevention of varicella-zoster virus infection: Herpes zoster](#)", section on 'Adults ≥60 years of age'.)

Zoster vaccination is recommended for individuals who are 60 years of age or older. Immunization is contraindicated in HIV-infected patients with a CD4 T-cell count <200 cells/mm<sup>3</sup>. (See "[Prevention of varicella-zoster virus infection: Herpes zoster](#)" and "[Immunizations in HIV-infected patients](#)".)

**SUMMARY AND RECOMMENDATIONS**

- Varicella zoster virus (VZV) infection of cerebral arteries produces a vasculopathy, manifesting most often as ischemic stroke and less often as hemorrhagic stroke. Vasculopathy can occur after either varicella or herpes zoster. (See ['Introduction'](#) above.)
- The likely mechanism by which VZV causes stroke is by direct infection of cerebral arteries, which leads to a spectrum of both inflammatory and noninflammatory pathological changes including thrombosis, necrosis, dissection, and aneurysm formation. (See ['Pathogenesis'](#) above.)
- VZV vasculopathy usually manifests as ischemic stroke, but can also produce aneurysm, subarachnoid and cerebral hemorrhage, arterial ectasia, and carotid dissection. Patients may also have a history of recent zoster or varicella. (See ['Clinical manifestations'](#) above.)
- VZV vasculopathy involves both large and small arteries. Brain imaging typically shows ischemic or hemorrhagic infarctions at gray-white matter junctions. (See ['Imaging'](#) above.)
- A modest mononuclear pleocytosis on cerebrospinal fluid analysis is seen in approximately two-thirds of patients with VZV vasculopathy. (See ['Cerebrospinal fluid testing'](#) above.)
- VZV vasculopathy may be clinically suspected in a patient who presents with a stroke and has had a recent history of shingles. Supportive data include a mononuclear pleocytosis on CSF testing and MRI findings consistent with a hemorrhagic or ischemic lesion in gray-white matter junctions. The diagnosis is confirmed by testing for anti-VZV antibodies or VZV DNA in the CSF. (See ['Diagnosis'](#) above.)
- For patients with suspected VZV vasculopathy who are awaiting their CSF laboratory testing results, we suggest empiric IV [acyclovir](#) ([Grade 2C](#)). A reasonable regimen is 10 to 15 mg/kg three times daily for a minimum of 14 days. We also suggest a short course of oral [prednisone](#) (1 mg/kg daily for five days) without a steroid taper ([Grade 2C](#)). (See ['Treatment'](#) above.)
- As of November 2012, there is a shortage of IV [acyclovir](#) in the United States due to a manufacturing delay [[45,46](#)]. Clinicians should check the [US Food and Drug Administration's website](#) for information about the availability of IV acyclovir. If IV acyclovir is not available, an alternative IV regimen can be used. Specific recommendations are presented separately. (See ["Acyclovir: An overview", section on 'Acyclovir shortage'](#).)

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