Central Nervous System Vasculopathy In Varicella Zoster Virus Infection

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Varicella zoster virus (VZV) is an exclusively human double-stranded DNA virus that is the causative factor for two ubiquitous conditions: varicella in children and zoster in adults. Both conditions are associated with neurological complications. Centripetal trans-axonal spread via cranial nerve ganglia appears to afford entry into the central nervous system. There is increasing evidence of varicella zoster virus playing a role in the development of giant cell arteritis. First associated with transient ischemic attacks and ischemic strokes, vasculopathy secondary to varicella zoster virus infections has now been associated with aneurysms that may or may not lead to subarachnoid hemorrhage, multifocal vasculitis, arterial dissection, dolicoectasia, cortical venous sinus thrombosis, ischemic cranial neuropathies and spinal cord infarction. Prior knowledge of the myriad clinical manifestations helps in early diagnosis and treatment of the complications.

Keywords: Varicella Zoster virus; Vasculopathy; Stroke

Abstract

Varicella zoster virus is an exclusively human double-stranded DNA virus that is the causative factor for two ubiquitous conditions: varicella in children and zoster in adults. Both conditions are associated with neurological complications. Centripetal trans-axonal spread via cranial nerve ganglia appears to afford entry into the central nervous system. There is increasing evidence of varicella zoster virus playing a role in the development of giant cell arteritis. First associated with transient ischemic attacks and ischemic strokes, vasculopathy secondary to varicella zoster virus infections has now been associated with aneurysms that may or may not lead to subarachnoid hemorrhage, multifocal vasculitis, arterial dissection, dolicoectasia, cortical venous sinus thrombosis, ischemic cranial neuropathies and spinal cord infarction. Prior knowledge of the myriad clinical manifestations helps in early diagnosis and treatment of the complications.

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Background

Varicella zoster virus (VZV) is an exclusively human, neurotropic double-stranded DNA virus alpha herpesvirus. VZV vasculopathy was first described in 1896 by Baudouin and Lantuejoul who described stroke following VZV infection [1].

There is strong evidence that VZV infection is a risk factor for strokes [2-9]. VZV vasculopathy is seen in both immunocompetent and immunocompromised persons and can follow either varicella or zoster infection, as a result of which, populations at the extremes of age are more commonly affected. The central nervous system is the most common extracutaneous site of involvement in varicella, and VZV vasculopathy has been proposed to account for as many as a third of all ischemic strokes in children [10].

Etiopathogenesis

VZV vasculopathies point to active viral replication [11] which is reflected by the presence of multinucleated giant cells, Cowdry A inclusion bodies and viral particles, and VZV antigen and DNA in the blood vessels [12]. Several studies have demonstrated the presence of afferent fibres from certain cranial nerve ganglia to both intra- and extra-cranial blood vessels, which can provide an anatomical pathway for the trans-axonal spread of virus [12] to the cerebral vasculature. Infected cerebral arteries demonstrate thickening of the tunica intima with proliferation of myofibroblasts, depletion of smooth muscle cells and disruption of the internal elastic lamina [13]. In most cases, both small and large vessels are affected, followed by exclusive small vessel and large vessel disease respectively [14].

VZV Vasculopathy and Giant Cell Arteritis

Given the similar clinical and pathological features seen in VZV vasculopathy and giant cell arteritis (GCA), it has been postulated that there may be a role of VZV in the pathogenesis of GCA [15-18]. The study by Gilden et al. [19] has shown the presence of VZV antigen in 74% patients of temporal artery biopsy-proven GCA versus 8% in normal temporal arteries (p<0.0001), while Nagel et al. [20] found the proportions to be 64% and 22% respectively (p<0.001). Gilden et al. have also found the prevalence of the VZV antigen in patients with a clinical and serological feature of GCA (with or without a positive temporal artery biopsy) in significantly higher numbers compared to those without [19]. Based on these observations, VZV appears to trigger the immunopathology of a significant subset of GCA and antiviral treatment is likely to confer benefit in addition to corticosteroids [21].

Clinical Manifestations

Initially associated with TIA and stroke, predominantly ischemic, neurovascular involvement in VZV infection can manifest with aneurysmal dilatation of arteries that can result in subarachnoid hemorrhage, multifocal vasculitis, arterial dissection and dolicoectasia, ischemic cranial neuropathy, and as stated above, temporal arteriopathy resembling GCA, spinal cord infarction and even cerebral venous sinus thrombosis [22]. In adults, neurovascular involvement typically presents with focal neurological deficits related to the area of the CNS (Central Nervous System) involved, a few weeks after the onset of cutaneous varicella or herpes zoster [23], although in one-third of patients with virologically verified VZV vasculopathy, there may be no preceding rash [14]. In children, stroke following varicella usually presents as an acute hemiparesis on average 4 months after rash [24]. The clinical course of VZV vasculopathy is often protracted, generally lasting weeks to months [25].

Investigations

Investigations include CSF studies and neuroimaging. A predominantly mononuclear pleocytosis, with the cell count not typically crossing a hundred, is seen in two-thirds of patients with VZV vasculopathy [14]. As with the rash, CSF pleocytosis is absent in approximately one-third of the cases. Nagel and colleagues studied the
CSF samples of 14 patients with VZV vasculopathy and found anti-VZV IgG (including a reduced serum to CSF antibody ratio, indicating intrathecal production) in almost all samples, whereas the VZV DNA was detected in only around 30%; this has been attributed to the protracted clinical course of VZV vasculopathy [14,26]. Only CSF negative for both VZV DNA and anti-VZV IgG antibody can reliably exclude the diagnosis of VZV vasculopathy [25]. On imaging, both cortical and deep-seated FLAIR hyperintensities can be seen; lesions at the gray-white matter junctions in particular, some of which enhance, provide strong supportive evidence to VZV as the cause of disease [27,28]. In the study by Nagel et al. stated earlier, the prevalence of rash, CSF pleocytosis or vascular abnormalities on MRA/conventional angiography were seen in two thirds of the patients, while abnormalities on CT/MRI were seen in almost all patients with VZV vasculopathy [14].

Treatment and Prevention

Antivirals and steroids form the mainstay of treatment of VZV vasculopathy. There have been no prospective trials to determine the optimum treatment regimen, but Gilden et al. have recommended using IV acyclovir 10 mg/kg to 15 mg/kg TID for at least 14 days [11]. Short courses of prednisone, at a dose of 1 mg/kg, have been used concurrently for presumed cerebral arterial inflammation and the possible role of VZV triggering the immunopathology for GCA [11,29]. However, caution should be taken if steroids are continued beyond 5 to 7 days given the theoretical risk of viral infection potentiation. Patients treated with antivirals had significantly reduce risk of stroke after VZV infection [2]. Immunosuppressed patients often require longer duration of antiviral treatment, for which oral valacyclovir has been employed [11].

The use of vaccines for the prevention of complications of VZV is controversial. There have been few reports of ischemic stroke in children following varicella vaccination [30,31] and several reports of meningitis post-vaccination [32]. The hypothesis is that the live attenuated virus used in the vaccines can cause vasculopathy after an initial latent period in the peripheral ganglia by reactivation; this phenomenon is seen in children rather than adults, since they are not immune to VZV [30,31]. Interestingly, Langan et al. have compared patients (aged 65 years and higher) with herpes zoster who were given the VZV vaccine within the week prior to or after infection, versus those who were not vaccinated, and found the 6-month risk of stroke to be lower in the former group [2]. Sufficient data is lacking from other age groups to confirm if this discrepancy in outcomes is real or just incidental.

Conclusions

In summary, VZV vasculopathy is a complication of dermatologic infection that can follow both varicella and herpes zoster. Clinical manifestations are typically, but not limited to, transient ischemic attacks and ischemic strokes. VZV vasculopathy is suspected in patients who develop a focal neurological deficit in temporal association with the classical dermatologic VZV infections, with supportive evidence from CSF and imaging studies. Antivirals, with or without steroids, form the mainstay of treatment.

References


