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Virus Vasculopathy and Stroke: An Under-Recognized Cause and Treatment Target

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Abstract

While arteriosclerotic disease and hypertension, with or without diabetes, are the most common causes of stroke, viruses may also produce transient ischemic attacks and stroke. The three most-well studied viruses in this respect are varicella zoster virus (VZV), cytomegalovirus (CMV) and human immunodeficiency virus (HIV), all of which are potentially treatable with antiviral agents. Productive VZV infection in cerebral arteries after reactivation (zoster) or primary infection (varicella) has been documented as a cause of ischemic and hemorrhagic stroke, aneurysms with subarachnoid and intracerebral hemorrhage, arterial ectasia and as a co-factor in cerebral arterial dissection. CMV has been suggested to play a role in the pathogenesis of arteriosclerotic plaques in cerebral arteries. HIV patients have a small but definite increased incidence of stroke which may be due to either HIV infection or opportunistic VZV infection in these immunocompromised individuals. Importantly, many described cases of vasculopathy in HIV-infected patients were not studied for the presence of anti-VZV IgG antibody in CSF, a sensitive indicator of VZV vasculopathy. Unlike the well-documented role of VZV in vasculopathy, evidence for a causal link between HIV or CMV and stroke remains indirect and awaits further studies demonstrating productive HIV and CMV infection of cerebral arteries in stroke patients. Nonetheless, all three viruses have been implicated in stroke and should be considered in clinical diagnoses.

Keywords

Virus vasculopathy; VZV; HIV; CMV

VIRAL CAUSES OF STROKE

Stroke is a common cause of mortality and morbidity worldwide [1]. While established risk factors, such as hypertension, diabetes, obesity and hypercholesterolemia have been identified and are targets for stroke prevention, viral infections have also emerged as risk factors for stroke. Identification of viruses that directly cause stroke, as evidenced by direct invasion of cerebral arteries corresponding to areas of infarction, would provide therapeutic targets for stroke prevention. Varicella zoster virus (VZV), human immunodeficiency virus (HIV) and cytomegalovirus (CMV) have all been associated with stroke. However, VZV is

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CONFLICT OF INTEREST

All authors report no conflict of interest.

the only virus that has been shown to directly invade cerebral arteries and produce vasculopathy [2]. Herein, we review evidence regarding the association of these three viruses with stroke.

VZV VASCULOPATHY

VZV (human herpesvirus 3) is a ubiquitous, exclusively human DNA virus. Primary infection occurs via respiratory aerosols or contact with vesicles from an infected individual and results in the characteristic disseminated rash of varicella (chickenpox). Subsequently, VZV becomes latent in ganglionic neurons in cranial nerve ganglia, dorsal root ganglia and autonomic ganglia along the entire neuraxis [3–8]. A decline in VZV specific cell-mediated immunity in elderly and immunocompromised individuals results in virus reactivation in one or more ganglia [9–12]. VZV reactivation most commonly manifests as herpes zoster (shingles), frequently complicated by postherpetic neuralgia. Less often, VZV reactivation leads to retinal necrosis [13], myelopathy [14] and vasculopathy [15] or even chronic radicular pain without rash, also known as zoster sine herpette [16,17].

The incidence and prevalence of stroke caused by VZV is unknown, although estimates in children reveal that varicella accounts for 7 to 31% of arterial ischemic stroke [18,19], with 1 in 15,000 cases of varicella associated with stroke [18]. In transient cerebral arteriopathy of childhood, stroke is preceded by varicella in 44% of cases [20]. In adults, VZV vasculopathy is more common in immunocompromised than in immunocompetent individuals. In immunocompromised adults, VZV infection of the central nervous system (CNS) was detected in 1.5 to 4.4% of autopsy cases [21–23]. In postmortem studies of HIV-infected individuals, VZV vasculopathy occurred more frequently late in the course of infection when there was significant CD4+ depletion [24,25].

CLINICAL FEATURES AND DIAGNOSIS

In adults, the typical clinical presentation of stroke caused by VZV is the occurrence of ophthalmic-distribution herpes zoster followed by acute contralateral hemiplegia weeks to months later [26] or, in children, varicella followed by acute hemiplegia. However, since VZV can affect both large and small arteries resulting in ischemic or hemorrhagic strokes, clinical presentations may vary and include headache, mental status changes, aphasia, ataxia, hemisensory loss, hemianopia and even monocular visual loss [27,28]. Many patients experience transient ischemic attacks with protracted neurological symptoms and signs. Importantly, 37% of VZV vasculopathy cases do not have the characteristic varicella or zoster rash [15]. Furthermore, if rash occurred months before the stroke, it may not be regarded as related. Thus, it is imperative that the diagnosis of VZV vasculopathy be considered in all strokes of unclear etiology, particularly in HIV-positive and other immunocompromised patients.

Brain imaging of patients with VZV vasculopathy reveals ischemic or hemorrhagic infarction in virtually all cases. An analysis of 30 cases of virologically confirmed VZV vasculopathy revealed changes in all but one subject who had only posterior ciliary artery involvement [15,29]. MRI typically shows superficial and deep-seated lesions, in both gray and white matter, and particularly at gray-white matter junctions (Fig. (1)), providing a clue to the cause of disease. Lesions may be bland or hemorrhagic and may enhance. While 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.

Typical angiographic changes include segmental constriction, often with poststenotic dilatation (Fig. (2)). In addition to arterial occlusion, aneurysm and hemorrhage can also

develop. In the largest series (30 patients) reported to date with virologically verified VZV vasculopathy, 23 patients underwent vascular studies (conventional angiography or magnetic resonance angiography) and 16 (70%) of those showed vascular abnormalities [15]. Brain imaging and vascular studies revealed mixed large and small artery involvement in 15 (50%), pure small artery involvement in 11 (37%) and pure large artery disease in 4 (13%) patients. 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, while pure large artery disease occurs least often.

Cerebrospinal fluid (CSF) abnormalities are common. A modest pleocytosis, usually less than 100 cells and predominantly mononuclear, is seen in about two-thirds of patients with VZV vasculopathy [15], and many patients also have red blood cells in their CSF. CSF protein is usually elevated, while glucose is normal. Oligoclonal bands are frequently present and have been shown to be VZV-specific IgG [31].

When a clinical diagnosis of VZV vasculopathy is suspected and supported by single or multiple characteristic lesions on MRI or CT, virological confirmation is required. The diagnostic value of detecting anti-VZV immunoglobulin (Ig) G antibody in CSF is greater than that of detecting VZV DNA [32]. In the largest series of virologically verified VZV vasculopathy from multiple institutions in the United States, Europe and Japan, 28 of 30 (93%) patients with VZV vasculopathy had anti-VZV IgG in the CSF compared to only 30% with VZV DNA in CSF [15]. Although a positive PCR for VZV DNA in CSF is helpful, a negative PCR does not exclude the diagnosis; only negative results in both VZV PCR and anti-VZV IgG antibody tests in CSF can reliably exclude the diagnosis of VZV vasculopathy.

Importantly, many of the same symptoms, signs, CSF, imaging and arteriographic abnormalities that occur in VZV vasculopathy are seen in primary angiitis of the nervous system and the granulomatous angiitides such as CNS sarcoidosis, neurosyphilis, and tuberculous and fungal infections of the nervous system. 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.

Because VZV vasculopathy is caused by productive viral infection in arteries, all patients are typically treated with intravenous acyclovir based on Category 3 evidence (opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees). In the study of 30 patients [15], patients treated with acyclovir alone improved or stabilized, compared to 75% who improved or stabilized when treated with both acyclovir and steroids. Because patients received different treatment regimens at different institutions in an uncontrolled setting, the determination of 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, 10–15 mg/kg three times daily for a minimum of 14 days. Since there is often an inflammatory response in infected cerebral arteries, we also give oral prednisone, 1 mg/kg daily for 5 days; no taper is needed. Importantly, we never treat patients with VZV vasculopathy with steroids for more than 1 week since long-term treatment can potentiate virus infection. Finally, we have encountered multiple patients with VZV vasculopathy who continue to

have neurologic symptoms after intravenous acyclovir treatment. Most, but not all of these patients were HIV-positive or had AIDS; one patient was diabetic. In these situations, we have recommended oral valacyclovir, 1 gram three times daily for an additional 1 to 2 months, which resulted in clinical improvement.

PATHOGENESIS

The mechanism by which VZV causes stroke is likely by direct infection of cerebral arteries, leading to thrombosis, necrosis, dissection and aneurysm. Studies in cats 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 [33–35]. Pathological and virological analyses of cerebral arteries of patients who died of VZV vasculopathy have revealed herpes virions [36,37], VZV antigen and VZV DNA [2,23,25,38–41] in the walls of cerebral arteries (Fig. (3)).

A potential cofactor that has emerged in VZV-associated ischemic stroke is the role of transient autoantibodies to phospholipids and coagulation proteins during or after varicella [43,44]. Both the presence of lupus anticoagulant and protein S deficiency were found in a child with disseminated intravascular coagulation during varicella [45]. Another report described a child with varicella who had protein S deficiency along with the presence of anti-protein S antibody and hypercoagulability, supporting a pathogenic role for antibody [46]. Recently, Massano *et al.* [47] described an adult with varicella who developed stroke and multiple peripheral thrombotic events associated with transient protein S deficiency and transient anticardiolipin and anti-beta 2 glycoprotein antibodies. The role of these autoantibodies in thrombus formation in cerebral arteries during VZV infection requires further study.

Overall, VZV vasculopathy usually manifests as ischemic stroke but can also produce aneurysm, subarachnoid and cerebral hemorrhage, arterial ectasia and carotid dissection. In such patients, the clinician should ask whether there is a history of recent zoster or varicella rash, and if so, should undertake virological analysis for VZV. Because not all patients with VZV vasculopathy have a history of zoster or varicella rash, the CSF of all patients with uni- or multifocal vasculopathy, as well as CNS angiitis of unknown etiology, should be studied for the presence of both VZV DNA and anti-VZV IgG antibody. Rapid and accurate diagnosis can lead to effective antiviral treatment of VZV vasculopathy.

CYTOMEGALOVIRUS (CMV) VASCULOPATHY

Human CMV typically becomes latent early in life in myeloid precursor cells after asymptomatic infection. CMV does not usually cause disease in immunocompetent individuals; however CMV infection in immunosuppressed organ transplant recipients and AIDS patients is a major cause for concern [48]. Since aggressive prophylaxis treatment of heart transplant recipients with ganciclovir and CMV hyperimmune globulin has decreased cardiac allograft vasculopathy, a major cause of transplant failure, CMV has been linked to vascular changes in solid organs after transplantation [49,50]; nevertheless, an association between CMV and vasculopathy in immunocompetent subjects remains unclear. CMV antigen was originally detected in 7 of 26 cell cultures derived from atherosclerotic plaques [51]. Subsequently, the titer of circulating antibody against CMV was found to be higher in subjects undergoing vascular surgery for atherosclerosis than in matched control subjects [52]. Those studies suggested an association between CMV and vascular disease, a hypothesis supported by the finding of CMV DNA in arterial walls within atherosclerotic plaques [53]. Primary tissue cultures containing vascular smooth muscle cells are permissive for CMV infection, during which significant amounts of pro-inflammatory adhesion molecules are synthesized [54,55]. Further, 5-lipoxygenase gene transcription is induced in

vascular smooth muscle cells infected with CMV [56]; 5-lipoxygenase initiates synthesis of leukotrienes, which are mediators of cardiovascular disease, from arachidonic acid. Thus, CMV replication in arterial endothelial cells may induce an atherosclerotic environment, restricting blood flow and promoting ischemic stroke. However, correlation between artery wall thickening and CMV is not conclusive [57]. In addition, a prospective study involving >600 apparently healthy men found no correlation between anti-CMV IgG and an increased risk of atherosclerosis [58], and CMV does not induce neointimal hyperplasia [59]. In an organ culture model of CMV infection of human renal arteries, infectious virus was recoverable from supernatants up to 144 days post-infection; endothelial cells were the first to become infected, after which virus penetrated into the media [60]. Overall, circumstantial evidence suggests a mechanism by which abortive or active CMV replication in arterial cells may lead to stenosis, although continued studies are required to demonstrate a direct causal link between CMV arterial infection and stroke.

HIV VASCULOPATHY

HIV infection of humans worldwide has resulted in more deaths than any other infectious disease. Nevertheless, analysis of stroke in adult AIDS patients from the Edinburgh HIV Autopsy Cohort [61] revealed that infarcts in HIV-infected patients are rare in the absence of cerebral non-HIV infection, lymphoma or embolism; in fact, an HIV-associated vasculopathy was found in only 5.5% of all cases studied. Lesions in all cases were characterized by hyaline small-vessel thickening, perivascular space dilatation, and rarefaction with vessel wall mineralization; perivascular inflammatory cell infiltrates were seen in some cases. Later, the incidence of cerebrovascular events and stroke in HIV-infected patients ages 15 to 44 years was found to be 9 to 12% [62]. In another study, which included data from ultrasonography, brain CT, MRI, CSF and blood analysis from 1087 stroke subjects, 6% were found to be infected with HIV [63], compared to an earlier longitudinal neuroradiological study of 68 HIV-positive children that revealed an incidence of stroke at 1.3% per year [64]. Direct association of HIV with stroke was impossible because HIV was not detected in cerebral arteries. Since HIV infection is immunosuppressive, other opportunistic infections, such as VZV must be considered.

Among reports that attribute the sole cause of vasculopathy to HIV is a case study of a 5-year-old boy with AIDS who developed transient vasculopathy that resolved after therapy with only aspirin and HAART; the patient was PCR-negative for multiple viruses including VZV, although no studies were done to detect anti-VZV IgG in CSF [65]. Another case report [66] described a 33-year-old HIV-positive man with rapidly progressive vasculopathy and recurrent strokes, a very high HIV load, and normal CSF. The patient was studied for cryptococcal antigen, syphilis and toxoplasmosis, all of which were negative; after HAART therapy, the patient improved and the HIV load became low. There was no indication that any studies for VZV were performed in this patient. A third instance of successful treatment of HIV-associated vasculopathy with HAART was described in a 49-year-old man [67]. The CSF contained 18 cells, primarily mononuclear, and no testing for Myco-bacteria or fungal infection was found. Although PCR was negative for multiple viruses including VZV, no testing for anti-VZV antibody in CSF was performed. Overall, conclusions about the usefulness of HAART in treating cerebral vasculopathy in HIV-infected patients await additional studies, especially since HIV, unlike VZV, has not yet been shown to be directly involved in cerebral vessels.

An analysis of three HIV-infected patients who developed intracranial aneurysms did not identify an etiologic agent [68]. None of the patients was studied for VZV, which was unfortunate since numerous cases of VZV vasculopathy with aneurysm have been described in adults and children [reviewed in Gilden *et al.*, ref. 42]. Nevertheless, direct involvement

of HIV in aneurysm formation has been suggested by monoclonal anti-gp41 antibody staining in the aneurysmal arterial wall in a 6-year-old boy with AIDS [69]. A larger analysis of 67 HIV-infected patients with stroke revealed vasculopathy that was both extracranial or intracranial with and without fusiform aneurysmal dilatation, stenosis and variation in the caliber of vessels; again, none of the HIV-positive stroke group was studied for antibody to VZV [63].

The studies above raise the possibility that stroke in HIV patients may actually represent a VZV vasculopathy for which an adequate evaluation was not performed. For example, Tipping and colleagues [70] described a 27-year-old HIV-infected woman who presented with stroke and a CD4 count of 14 cells/ μ l and who demonstrated fusiform aneurysmal dilation of the left internal carotid artery and left middle cerebral artery upon imaging. Although VZV vasculopathy, even in the absence of VZV rash, was a likely strong possibility in light of her immunosuppressed state, cerebral artery pathology and the presence of a CSF pleocytosis, the patient's CSF was not tested for VZV DNA or anti-VZV IgG antibody, nor were her affected cerebral arteries tested for VZV antigen staining [71]. At autopsy, HIV p24 antigen was not found in the affected cerebral arteries. In another example, Kossorotoff and colleagues [72] described a 32-year-old HIV-infected man who presented with stroke and multiple ectasias and focal stenoses of medium and small cerebral arteries with a CSF pleocytosis. His history was remarkable for recurrent herpes zoster. His CSF did not contain VZV DNA, but the more sensitive test to diagnose VZV vasculopathy, i.e., detection of anti-VZV IgG antibody in CSF [32,73], was not carried out. Thus, this too might well have been a VZV vasculopathy in an HIV patient. Overall, HIV patients with stroke should have their CSF tested for both VZV DNA and anti-VZV IgG antibody. If the cause of vasculopathy is still unknown at death, the cerebral arteries should be analyzed for the presence of both VZV DNA and VZV antigen.

There is some indirect evidence that HIV might infect arteries. Premature coronary disease has been reported in HIV patients receiving protease inhibitors [74], leading to the notion that HIV disease might be atherogenic [74,75]. HIV infects specific cell types in humans such as helper T (CD4+) cells, macrophages and dendritic cells. Immunohistochemistry had detected HIV-infected dendritic cells (p24+) in atherosclerotic lesions in aortas of AIDS patients, and considerably more HIV-positive cells were found in the atherosclerotic lesions in the diseased aorta compared to the non-diseased aortic segments [76]. Furthermore, the CXCR3 chemokine receptor, which is important for HIV attachment, was also detected by immunofluorescence and immunohistochemistry in areas associated with atherosclerotic plaques in arterial endothelial and smooth muscle cells. CXCR3-positive astrocytes and cerebellar purkinje cells were also prominent in the CNS of HIV-positive patients [77]. To test the possibility that HIV infects smooth muscle cells which in turn could accelerate vascular disease, Eugenin *et al.* [78] used confocal fluorescence microscopy with antibodies specific for the HIV p24 protein and smooth muscle α -actin to analyze tissue sections from atherosclerotic plaques of HIV-positive humans; the p24 protein colocalized with smooth muscle α -actin in the smooth muscle layer of arteries with plaque, although non-atherosclerotic arteries of HIV patients, which should not contain p24, were not analyzed.

HIV sequences were detected by *in situ hybridization* in sections of the intima and media of the anterior descending artery from an individual with HIV-associated coronary arteritis who died of myocardial infarction [79]. Extensive vasculopathy has also been demonstrated in transgenic mice carrying replication-defective HIV provirus [80]. In those mice, affected areas were composed primarily of T cells and occasionally plasma cells, but HIV gene expression was limited in affected areas. Finally, HIV-infected macrophages in transgenic mice were shown to have impaired cholesterol efflux, a condition that is highly atherogenic

[81]. Despite all the indirect evidence, an unequivocal association of HIV infection with stroke remains to be demonstrated.

SUMMARY

VZV, CMV and HIV have all been associated with stroke. Yet VZV is the only virus for which there is clear evidence of virus DNA and antigen in cerebral arteries corresponding to areas of ischemia or infarction. Antiviral therapy is indicated in VZV vasculopathy. While HIV and CMV have been found to infect smooth muscle cells in coronary or renal arteries, studies that demonstrate productive HIV or CMV infection of cerebral arteries in areas of ischemia/infarction are still lacking.

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ABBREVIATIONS

CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computerized tomography
HIV	Human immunodeficiency virus
Ig	Immunoglobulin
MRI	Magnetic resonance imaging
VZV	Varicella zoster virus

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Fig. 1. MRI scan of a patient with VZV multifocal vasculopathy
Proton-density brain MRI scan shows multiple areas of infarction in both hemispheres, particularly involving white matter. Arrows point to gray-white matter junction lesions. Reproduced from Gilden *et al.* [29] with permission from the Journal of NeuroVirology.

Fig. 2. Cerebral angiogram from a patient with VZV vasculopathy
Cerebral angiogram shows focal areas of stenosis (white arrows) and poststenotic dilatation (black arrows) involving the right posterior cerebral artery. Reproduced from Russman *et al.* [30] with permission from the American Medical Association.

Fig. 3. Pathological and virological findings in the arteries of patients who died from VZV vasculopathy

(A) A cerebral artery with multinucleated giant cells (arrow). (B) Multiple herpesvirions within a cerebral artery. (C) VZV DNA in the posterior cerebral artery (lane 3) and basilar artery (lane 5). (D) VZV antigen (red) in the media of a cerebral artery. Reproduced from Gilden *et al.* [42] with permission from the Lancet Neurology.