Published in final edited form as:

J Med Virol. 2018 August ; 90(8): 1283–1284. doi:10.1002/jmv.25201.

Heightened risk of ischemic stroke following recent herpes zoster ophthalmicus

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Keywords

herpes zoster; shingles; varicella-zoster virus; stroke; acyclovir; Valtrex; encephalitis; zoster vaccine

Strokes and stroke-related deaths are increasing around the world¹. Stroke is not a single entity. Stroke can be divided into two major groups: Ischemic stroke and hemorrhagic stroke. The majority of strokes are ischemic. Ischemic stroke is caused by a blocked blood vessel and hemorrhagic stroke is caused by a ruptured blood vessel. Ischemic stroke often requires an inflammatory process in a cerebral artery, which in turn leads to formation of a blood clot. The goal of this Commentary is to document increasing evidence that herpes zoster (shingles) can lead to stroke. The underlying hypothesis is that varicella-zoster virus (VZV) originating in the trigeminal ganglion (Cranial nerve V; Gasserian ganglion) can cause an inflammatory process in a cerebral artery, which in turn leads to occlusion of the affected artery and subsequent stroke.

A potential mechanism is illustrated in Figure 1. The childhood disease varicella (chickenpox) is characterized by a vesicular exanthem. Viral particles within the vesicles on the face are transported retrograde via sensory nerve fibers to the ophthalmic division of the trigeminal ganglion, where the VZV genome enters latency (arrow 1)². When the same child reaches late adulthood, VZV occasionally reactivates from the trigeminal ganglion, after which viral particles travel anterograde at a rate of ~0.5 cm/hr to the eye, to cause the distinctive illness herpes zoster ophthalmicus (HZO) (arrow 3)³. HZO accounts for 10–20% of all cases of herpes zoster. For every person who had varicella as a child, the lifetime risk of herpes zoster at any location is >30%.

What is less well known is that the ophthalmic branch of the trigeminal ganglion also sends afferent branches along the cerebral arteries, including the middle cerebral artery, anterior cerebral artery and internal carotid artery (Figure 1, arrow 2)⁴. The terminals of the nerve fibers enter the adventitia surrounding the arteries. Thereafter the virus then can enter the arterial wall, to initiate an inflammatory process⁵. In a recent immunohistochemical investigation of biopsies from temporal arteries, we found one artery biopsy from a woman with documented recent HZO that immunostained positively for herpes zoster antigen⁶.

Therefore herpes zoster in the trigeminal ganglia can lead to both HZO as well as an infection in an artery.

One of the earliest studies to report a statistical link between HZO and subsequent stroke was based on the Taiwan National Health Insurance Research Database between 2003–2005⁷. Out of a population of 22 million people, there were 658 patients identified with HZO. Of these 658 patients, 8.1% had a stroke within a year following HZO. In a larger age-matched control group that never had herpes zoster, only 1.7% had a stroke. In the HZO group, 81% of the strokes were ischemic. The current similar analysis from Iran included 105 cases of stroke and 105 controls⁸. When questioned about a retrospective diagnosis of herpes zoster in the prior 6 months, 24 stroke patients and 5 control patients had a history of herpes zoster. Among the 24 herpes zoster cases with stroke, 20 cases were considered to be ischemic stroke (84%) and 16 had prior HZO (67%).

A comprehensive meta-analysis of herpes zoster and stroke articles published in 2017 confirmed that patients with both HZO and zoster elsewhere on body were at significantly increased odds of stroke in the following year⁹. Yet, there remain confusing statistics in the literature about the relative risk of stroke after herpes zoster elsewhere in the body. Based on the pathogenesis model shown in Figure 1, stroke after HZO is directly related to virus-mediated pathology in the cerebral arteries. In contrast, there is no obvious pathogenetic mechanism to explain stroke after herpes zoster elsewhere in the body. Instead, herpes zoster elsewhere in the body may be a manifestation of generally depressed cellular immunity accompanying other conditions (and sometimes their treatments) associated with higher risk of stroke, such as diabetes mellitus, asthma, chronic obstructive pulmonary disease, and autoimmune diseases. In all studies in which both HZO and herpes zoster elsewhere on the body were linked with the risk of stroke, the risk with HZO was always higher.

With regard to anti-viral treatment, there appears to be no reduction of stroke by treatment of acute herpes zoster with the recommended one week of acyclovir or valacyclovir. Since stroke occurs more commonly after HZO, there may be value in a clinical trial to test whether a longer treatment regimen with valacyclovir will reduce the likelihood of subsequent stroke. Obviously, administration of herpes zoster vaccines (Zostavax; Shingrix) to older adults may prevent stroke secondary to HZO.

Finally, it is important to note that herpes zoster encephalitis is not synonymous with VZV vasculopathy. Some cases of encephalitis following herpes zoster, including zoster sine herpette, were initially misdiagnosed as a small glioma. Under this scenario, VZV exiting the neuronal fibers in the adventitia around the cerebral arteries enters the brain tissue, leading to circumscribed astrogliosis¹⁰. Correct diagnosis can require a brain biopsy with detection of both VZV proteins and VZV DNA. These patients are treated with valacyclovir for prolonged periods.

Acknowledgments

Reference 2 was written by a recipient of the Nobel Prize in Medicine in 1954. VZV research by the author was supported by NIH grant AI89716.

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Figure 1.

Herpes zoster ophthalmicus and stroke. The three branches of the trigeminal ganglion are shown on the left. When a child contracts varicella during childhood, VZV travels via sensory nerves from the exanthem on the face to the ophthalmic branch of the trigeminal ganglion, where the virus enters a latent state. (Arrow 1) During late adulthood, the virus occasionally reactivates in the same ganglion and travels to an eye, to cause herpes zoster ophthalmicus. (Arrow 3) The virus may also travel to nerves that surround some of the cerebral arteries. (Arrow 2)