There are now 9 human herpesviruses (HHVs); the increase from 8 to 9 was caused by a recent decision to split HHV strains 6A and 6B into distinct species. The 9 species are subdivided into 3 subfamilies: alpha (herpes simplex virus [HSV]), beta (cytomegalovirus, HHV6A, HHV6B, and HHV7), and gamma (Epstein-Barr virus and Kaposi sarcoma–associated herpesvirus [sometimes called HHV8]). These same herpesviruses have evolved with humankind around the world since the great migration of modern humans across the Mandeb Strait out of Africa ~60 to 100 thousand years ago.1 In a report in this issue of Circulation, Elkind et al2 sought to determine whether any of 5 herpesvirus infections—HSV1, HSV2, VZV, cytomegalovirus, or Epstein-Barr virus—increased the risk of arterial ischemic stroke (AIS) in children ≤18 years of age. They conclude that HSV1 infection and, to a lesser extent, VZV infection may act as triggers for childhood AIS. This editorial examines the biological plausibility of that assertion on the basis of both a literature review and the known pathogenesis of infection with HSV, VZV, and the live attenuated varicella vaccine virus.

VZV and HSV Antibody Testing

There is a major problem with the varicella antibody testing in this study. The authors selected a commercial VZV ELISA test to measure serum IgM and IgG antibodies. The commercial ELISA kits have been proven to be too insensitive to detect varicella antibody induced by varicella vaccination since the original clinical trials of varicella vaccination conducted in the United States in the 1980s.4 The commercial IgM testing kits are even more insensitive than the commercial IgG testing kits. Because many immunized children never develop antibodies detectable by the commercial kits, the numbers (and percentages) of children with negative VZV titers in Tables 2 and 3 are not valid; in other words, many of the immunized children with negative VZV titers would have positive titers by more sensitive assays. Here is a specific example: There were 274 patients with AIS from North America and Australia. Because of universal varicella immunization, at least 247 of these patients should have been positive for VZV antibody, assuming a 90% seroconversion rate after varicella vaccination (especially in children who had received 2 varicella vaccines). However, the authors found VZV IgG antibody in only 182 patients with AIS from their entire cohort of 326 patients from the 9 countries (Table 2).3

In future studies, varicella antibodies must be measured by more sensitive assays; the 2 assays that are available are FAMA (fluorescent antibody against membrane antigen) and glycoprotein ELISA assay. Titers by both assays correlate with neutralization titers.5,6 Although neither assay is commercially available, the Centers for Disease Control and Prevention and other virology research laboratories have adapted these assays to measure anti-VZV antibody titers in children in the United States. For all these reasons relating to their ELISA testing methodology, the authors may have missed any association between live attenuated varicella vaccination and AIS or, conversely, any protection of varicella vaccination against AIS.

There is also a potential problem with the HSV ELISA testing kits. In Table 3, the authors report that 32 patients had positive IgM antibodies to HSV1, whereas no patient had positive IgM antibodies to HSV2. What is puzzling about

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Biological Plausibility of a Link Between Arterial Ischemic Stroke and Infection With Varicella-Zoster Virus or Herpes Simplex Virus

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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the subsequent HSV data is that 48 children had IgM antibodies that were indeterminate between HSV1 and HSV2. In the Materials section in the online-only Data Supplement, the authors state that they used an HSV antibody testing kit called HerpeSelect (Focus Diagnostics), which can differentiate IgG antibodies to HSV1 from antibodies to HSV2. The HerpeSelect IgG test also may be more sensitive than standard HSV IgG ELISA testing kits. However, even with the respected HerpeSelect assay, they were not able to detect low levels of IgG antibody to either HSV1 or HSV2 in the 48 children with indeterminate HSV IgM antibody. Among a total enrolled population of 326 children with AIS and 115 control subjects (up to 19 years of age), it is noteworthy that not a single child or adolescent had a positive HSV2 IgM test by their ELISA assays (Table 3).

VZV and HSV Neuropathogenesis and Conclusions

The neuropathogenesis of stroke after VZV infection has been investigated more than stroke after HSV infection (Figure 2). The basic pathogenesis of varicella includes a viremia by which the virus travels in lymphocytes to the skin to cause the characteristic exanthem. Even though the varicella vaccine virus is greatly attenuated, there is a brief viremia in some recipients. Thus, both wild-type and vaccine virus could cause an arteritis by direct invasion of arteries. However, because the average length of time between wild-type varicella and stroke is 18 weeks, the most likely mechanism involves establishment of a latent VZV infection in the trigeminal ganglion after varicella, followed by reactivation (herpes zoster with or without a rash) and viral spread to the arteries in the brain via sensory fibers from the trigeminal ganglion. Of note, varicella vaccine virus can also establish latency in and reactivate from the trigeminal ganglion. Because there are very few deaths after stroke in childhood, few cerebral arteries have not been examined for VZV DNA and antigens. However, many temporal arteries have been examined in biopsies from adults with giant-cell arteritis; both VZV DNA and VZV antigens have been detected (Figure 2). Furthermore, the serological response to herpes zoster definitely can include both IgM and IgG antibodies against VZV proteins. Thus, the biological possibility of VZV infection as a cause of cerebral arteritis appears highly likely (Figure 2).

Primary HSV1 infection presenting as gingivostomatitis has been associated with a viremia. After causing HSV gingivostomatitis, the virus enters the trigeminal ganglion and establishes a latent state. Because HSV also reactivates in the trigeminal ganglion, HSV could travel via efferent nerves into cerebral and temporal arteries. However, the data on HSV infection of arteries after HSV reactivation in humans are much more conflicting. As with VZV, HSV-specific IgM antibody responses after HSV reactivation have been seen. (As with VZV, the sensitivity of commercial ELISA IgM testing kits may vary.) There were few parental reports of a facial rash in the present report, which may suggest that subclinical reactivation rather than mild primary HSV1 infection is the
more likely infection being discovered by the authors’ IgM analyses.

In conclusion, Elkind et al certainly have provided serological evidence that HSV infection (probably either recent or reactivated) is associated with an increased risk of AIS, but they have not shown in this study that HSV infection acts as a trigger for AIS. Thus, the biological plausibility of HSV infection as a cause of arteritis needs further investigation. Although it may not yet be timely to start prolonged treatment with acyclovir, it certainly is timely to pursue further translational studies of this intriguing association between herpesvirus infection and AIS.

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None.

**References**

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