

Strokes and Infection With Varicella Zoster Virus

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(See the Major Article by Thomas et al on pages 61–8.)

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It was long assumed, before recent developments proved otherwise, that the presence of an infection with varicella zoster virus (VZV) was inevitably associated with a rash. We now know, due to the use of polymerase chain reaction (PCR) and other methods that have improved diagnosis, that patients can harbor infections with VZV even in the absence of cutaneous manifestations. Such “occult” VZV infections often affect the nervous and gastrointestinal systems. Central nervous system (CNS) VZV infections without rash were initially identified at autopsy [1] and subsequently in patients with meningitis through the PCR detection of VZV DNA in cerebrospinal fluid (CSF) [2]. Although there appears to be a relationship between VZV infection and arterial ischemic stroke (AIS) [3], these patients also do not display a rash when they develop symptoms involving the CNS.

In the current issue of *Clinical Infectious Diseases*, Thomas et al describe the connection between varicella and subsequent AIS in children. They used 4 large

databases and a self-controlled case series, analyzing data from strokes in the varicella cases. Data were analyzed 0–6 months after an episode of varicella and again at a later time. This method avoids confounding factors and is efficient at relating a rare condition, such as stroke in childhood, to a common infection, varicella, although it does not provide information on the absolute risk of post-varicella stroke. Thomas et al’s study revealed that in the 6 months following varicella, the incidence of childhood stroke is increased by a factor of approximately 4. There was no significant increase in strokes in adults after varicella, nor was there any increase in strokes 7–12 months after varicella in children. The pathogenesis of postvaricella stroke is not known, but VZV can infect cerebral arteries, which provokes inflammatory responses that damage the infected arteries and may lead to aneurysms [4–6]. Because the interval between an episode of varicella and a stroke can be as long as 6 months, reactivation of latent VZV acquired during varicella, rather than a smoldering persistent infection in arteries, seems more likely to cause AIS, although either possibility remains plausible. The VZV that infects arteries could be delivered from sensory neurons in which VZV reactivates or as a result of a viremia. It may well be that most strokes following varicella are, in reality, strokes following zoster without rash. When

one such stroke develops, there may be recurrences [7]. Strokes may also follow classic zoster, particularly when the ophthalmic branch of the trigeminal nerve is involved. It is conceivable that AIS after varicella in children is a manifestation of a rare defect in innate immunity described in certain severe alpha herpesvirus infections [8–12]. One mystery is why VZV would be at increased risk for reactivation soon after varicella. This timing may reflect the putative immunologic predisposition. Clearly, additional knowledge of the state of VZV prior to infection of cerebral arteries, as well as the immunologic status of the host who has experienced a VZV-induced stroke, is needed.

A relationship between zoster and stroke was appreciated before postvaricella stroke was recognized. At first termed giant cell arteritis, it now appears that this vasculitis syndrome is similar to what is termed VZV vasculopathy [13]. VZV vasculopathy may be a subset of giant cell arteritis. It was recognized historically that in the months following zoster, patients (usually adults) might manifest symptoms of stroke ipsilateral to the side of the body where zoster occurred.

Because strokes in children are unusual or rare, this increase in CNS disease from varicella, albeit serious to individuals, is not a major public health problem. The morbidity (which may be long-lasting)

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associated with strokes in childhood, however, makes childhood stroke a particularly important phenomenon to understand. The data of Thomas et al are similar to those reported in an earlier much smaller case-control study [14]; because of its magnitude, the study of Thomas et al provides significant confirmatory evidence for a causal relationship between varicella and stroke. An important next step would be to analyze possible effects of varicella vaccine on the incidence of childhood strokes. One published study of >3 million vaccinated children in the United States found no association with AIS within 1 month of vaccination [15].

Routine vaccination of children against varicella does not occur in the United Kingdom, where the current study was performed. Whether vaccination against varicella would lessen the risk of stroke can only be speculated upon, but if reactivation of VZV plays a role in production of strokes as has been postulated, vaccination might reduce this problem. In both immunocompromised and healthy children, reactivation of VZV is less common after vaccination than after varicella [16–18].

Vaccine policy in the UK may have been influenced against licensure of varicella vaccine because it is thought that children have to experience varicella to maintain circulating wild-type VZV to boost adult immunity and thus prevent waning immunity and consequent epidemics of zoster [19]. The incidence of zoster has been increasing in the United States, where varicella vaccine was licensed in 1995; however, zoster began its increase in the 1950s and has been increasing linearly since then [20]. The US increase in zoster thus is probably multifactorial and relates to an aging population, increased numbers of immunocompromised patients, and improved diagnostic methods, rather than simply universal varicella vaccination. Subclinical reactivation of VZV clearly occurs [21–25] and may boost immunity to the virus [26, 27]. Fears of epidemic zoster from routine vaccination against varicella may thus be

unfounded. Universal immunization has driven the incidence of varicella and its complications to vanishingly low levels in the United States, and the disease is now uncommon or rare [28]. The predicted epidemic of zoster since vaccine licensure has not materialized. It would be interesting to determine whether the incidence of childhood strokes has changed in the United States in the past 10–12 years.

It is now possible to determine whether AIS in a given patient may be due to VZV. Molecular methods are available for diagnosis, including PCR to identify VZV in CSF, immunofluorescence of VZV antigens in arterial biopsies, and the ratio between VZV antibodies in CSF and serum [4]. These diagnostic tests should be employed in patients who suffer AIS, not only for individual diagnosis, but also to understand better the nature and severity of postvaricella VZV-induced stroke as a problem. In countries where the varicella vaccine is used routinely, it is potentially possible to identify the vaccine strain (Oka) in CSF using PCR, as has been done in the very rare cases of VZV meningitis attributed to the vaccine type virus [2]. Although there have been at least 2 reports of stroke in children following vaccination [3], the vaccine strain was not identified in CSF in these children.

There is currently intensive interest in the United States in cases of VZV reactivation that occur without an accompanying rash. In addition to strokes, meningitis has been reported to be due to reactivation of VZV without rash [2]. The phenomenon of visceral zoster, affecting the gastrointestinal tract in the absence of rash, furthermore, may lead to achalasia, gastric ulcers, and intestinal pseudo-obstruction [29]. VZV achieves latency in the human gut, and therefore local reactivation might account for some of these conditions [30]. Whether universal varicella vaccination has lowered the frequency of these problems deserves further study.

In conclusion, VZV causes a wide variety of medical problems, including

AIS, in children, as shown in the Thomas et al study, and in adults. Varicella vaccine prevents severe or fatal varicella in healthy and immunocompromised individuals, and reduces the incidence of zoster. If strokes are due to reactivation of latent VZV, varicella vaccine might decrease the incidence of strokes because of its decreased propensity to cause reactivation disease. AIS might thus be yet one more reason to prefer vaccination to varicella in children.

Notes

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The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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