pediatric stroke

Original Research

Viral Pathogenic Mechanisms Leading to Stroke After Herpes Zoster Ophthalmicus in Children

Charles Grose, MD (1), Connor Sturges (2) and Heather J. Fullerton, MD, MAS (3)
(1,2) Division of Infectious Diseases/Virology Laboratory, Department of Pediatrics, University of Iowa, Iowa City, IA ; (3) Departments of Neurology and Pediatrics, University of California San Francisco, San Francisco, CA.

1.Correspondent: Dr. C. Grose, Professor
University of Iowa Hospital/room BT2001
200 Hawkins Drive
Iowa City, IA 52242
TEL: 319.356.2270
Email: Charles-grose@uiowa.edu

2. C. Sturges.
University of Iowa Hospital/room BT2001
200 Hawkins Drive
Iowa City, IA 52242
Email: csturges@cord.edu

3. Dr. H.J. Fullerton, professor
University of California San Francisco
675 Nelson Rising Lane
San Francisco, CA 94158
Email: Heather.Fullerton@UCSF.edu

Pediatr Stroke. 2024;85-115:
www.pediatricstrokejournal.com

pediatric stroke

Original Research

Copyright © belongs to author(s)

All rights reserved.

Any redistribution or reproduction of part or all of the contents in any form is prohibited other than the following:

- you may print or download to a local hard disk extracts for your personal and non-commercial use only
- you may copy the content to individual third parties for their personal use, but only if you acknowledge the website as the source of the material

You may not, except with our express written permission, distribute or commercially exploit the content. Nor may you transmit it or store it in any other website or other form of electronic retrieval system.

Abstract.

Viral infections in children are strongly associated with acute ischemic stroke, likely related to inflammatory effects on the coagulation system and vascular endothelium. In this review, we concentrate on a less common infection that may have a unique role in stroke pathogenesis: herpes zoster ophthalmicus (HZO). We postulate that HZO is the cause of stroke because of the following proposed neuropathogenesis. During a bout of varicella (chickenpox), varicella-zoster virus (VZV) is carried retrograde from nociceptive fibers in skin to the trigeminal ganglion, where the virus enters a latent state. Years later but still in childhood, after a stressful event such as cancer or immunosuppression with corticosteroids, VZV reactivates from latency and travels in afferent fibers not only to the eye (where the virus originated during varicella years earlier) but

also to the cerebral arteries innervated by the trigeminal ganglion. The resultant virus-induced inflammatory process leads to narrowing of the arterial lumen (arteriopathy) with eventual ischemic stroke. We performed a review of the published literature and identified 8 cases of childhood arterial ischemic stroke after HZO. Two cases occurred in infants who had first acquired VZV infection in utero, after the pregnant mothers had an active VZV infection. With regard to diagnosis, the cerebrospinal fluid in two cases of stroke after HZO were tested and found to be positive for VZV DNA. Therefore, a review of these 8 cases provides considerable insight into the relationship between VZV infection and subsequent stroke.

Key words: varicella-zoster virus; herpes simplex virus; congenital varicella; arterial ischemic stroke; focal cerebral arteriopathy; trigeminal ganglion

Introduction

The acute infectious disease that has been most strongly associated with pediatric stroke is varicella (commonly known as chickenpox)(1, 2). Varicella is the primary infection caused by

the herpesvirus varicella zoster virus (VZV)(3). VZV is one of 9 human herpesviruses. Herpesviruses are double-stranded DNA viruses, with a characteristic structure consisting of an inner capsid containing the genome surrounded by an amorphous tegument which in turn is covered by an envelope studded with viral glycoproteins; the diameter of a complete enveloped virion is around 200 nanometers (Figure 1). VZV has the smallest genome among the human herpesviruses encoding about 80 viral proteins(4). Herpesviruses are also notable in that they are among the most ancient of all viruses, having co-evolved with humankind in Africa(5, 6). This co-evolution over the millennia was only possible because all herpesviruses possess the interesting property called latency.

After primary infection, the virus is not eradicated by the adaptive immune system. Instead, VZV enters the sensory nerves and travels to the dorsal root ganglia (DRG) or the trigeminal nerve ganglion in the head, where it resides for the lifetime of the individual(3). Occasionally, if the individual undergoes a stressful condition such as cancer, or if the individual simply ages and the immune system undergoes senescence, the virus reactivates from latency in the DRG, travels anterograde in the same sensory nerves to cause the cutaneous disease known as herpes zoster (HZ; also called shingles). VZV also is the only member of the 9 human

herpesviruses, in which the primary infection (varicella) and the infection after reactivation (HZ) are two distinguishable diseases with separate names.

HZ was an evolutionary adaption that facilitated the preservation of the virus when humankind consisted of hunter-gatherer societies. If only one elderly person in a small social group had been infected with varicella as a child and developed herpes zoster as an adult, all younger individuals in the small group would contract varicella. Of importance for understanding the pathogenesis of pediatric stroke, herpes zoster also occurs in children and is also associated with subsequent stroke in children (see section below). This condition is far less common than stroke following varicella because herpes zoster is not a common illness in children. Nevertheless, the case reports of stroke following herpes zoster in children give considerable insight into the pathogenesis of some cases of pediatric stroke, especially the cases of herpes zoster ophthalmicus (HZO) where virus is known to originate in the trigeminal ganglion. Therefore, this association is the subject of a review.

We also include a most unusual report from England, in which a pregnant woman with herpes zoster in the third trimester delivered a newborn who had been infected in utero; this child

subsequently developed HZO and stroke in the first 2 years of life. This case suggests that maternal herpes zoster during pregnancy can confer risk for childhood stroke.

Stroke following herpes zoster ophthalmicus

The most complete epidemiologic study of HZ was carried out by Hope-Simpson in England within his own medical practice from 1947-1962(7). He found that the rate of HZ in 0-9 years old children was 0.7 cases per 1000 per year and the rate in 10-19 years old adolescents was 1.4 cases per 1000 per year. Around 15% of the cases were HZO. The current HZ rate in children would be considerably less in countries, such as the United States and Canada, which have had universal varicella vaccination for more than 20 years (8, 9). However, the rate of HZ in immunized children is not negligible because recipients of the varicella vaccine can present with HZ caused by the vaccine virus later in childhood or adolescence (10). Further, many countries have never implemented universal varicella vaccination, for example England and Ireland, most of Asia and the entire continent of Africa; therefore, varicella and HZ remain common illnesses around the world (11, 12). Because of the importance of HZO in our understanding of the pathogenesis of pediatric stroke, we analyze this association in the following paragraphs.

We performed a search of published medical literature using the search engines PubMed and Google Scholar and the following keywords: children, stroke, varicella, herpes zoster, encephalitis. After reviewing the manuscripts identified through this search, we identified a total of 8 pediatric arterial ischemic stroke cases following an infection of herpes zoster ophthalmicus (HZO); these are summarized in Table 1. The neurological symptoms associated with these cases included hemiparesis, facial palsy, aphasia, dysphasia, dysarthria, and hemidystonia. Based on the years when these cases occurred, all of the children would have had wild-type varicella infection (13-19). The last two cases (numbers 7 and 8) had an intrauterine varicella infection contracted from a VZV infection in the mother during gestation; those 2 cases are discussed in a separate section of this review (19). The median age for the first 6 cases was 7.9 years with a range of 4.6 to 14 years. Across all 6 cases, the infarct was ipsilateral to the HZO infection. The median interval between HZO onset and the stroke ictus was 17 weeks (range, 6 to 40 weeks). These 6 cases underwent cerebral angiography or magnetic resonance angiography which demonstrated abnormalities of the middle cerebral artery or anterior cerebral artery (Table 2), findings consistent with the childhood disease now known at focal cerebral arteriopathy (FCA).

A report of VZV DNA detected in the CSF of two of the 8 cases is of particular importance because this result indicates that viable virus was present in the CSF after the stroke(17). This finding increases the likelihood that the association of HZ with subsequent stroke is actually one of causation. Note that a majority of the case reports in Table 2 were published before VZV-specific PCR tests were widely available in clinical microbiology laboratories. VZV infection in the CSF is also detectable by the latest molecular technology of metagenomic next generation sequencing(20).

Stroke in infant with congenital varicella syndrome and postpartum HZO

Chickenpox in the pregnant woman is occasionally followed by in utero VZV infection of the fetus. The consequences of such an infection to the fetus may be minimal to inapparent; alternately, the newborn may present multiple congenital abnormalities. Laforet and Lynch (21)published the first report of a congenital defects syndrome in an infant who was born to a mother who had contracted chickenpox during week 8 of pregnancy. At birth, the infant was noted to have a malformed right leg and foot. Within the first 3 months of life, the baby manifested generalized cortical atrophy as well as chorioretinitis with bilateral optic atrophy.

Savage et al. (22)reported another infant with congenital defects born to a mother with a history of chickenpox during week 11 of pregnancy. This full-tern baby had a hypoplastic left arm with rudimentary digits. In 1975, Williamson published a review of the reported cases of congenital malformations associated with maternal chickenpox (23). She found that most involved the skin, eyes, and limbs, as was observed in the initial cases (Table 3). Three additional cases deserve special mention because they exemplify the importance of the trimester at the time of intrauterine infection. A report by Srabstein et al. (24)described a severely affected baby whose mother had chickenpox during the first trimester. Cuthbertson et al.(25) reported a case of congenital varicella syndrome which followed a second-trimester chickenpox infection in a pregnant woman. In contrast, only a mild case of the congenital syndrome was diagnosed in an infant born to a mother who had chickenpox in the third trimester (26). The incidence of congenital varicella syndrome is estimated to be about 2-3% in longitudinal studies of pregnant women with chickenpox(27, 28). The risk of the complete congenital syndrome is highest in the first 20 weeks of gestation.

Infants born after intrauterine VZV infection do not develop cellular immunity to the virus(29). Therefore, these infants are at high risk of reactivation and HZ in early childhood. Our case 7 is

an infant who was infected during the 8th month of gestation after maternal varicella(19). The infant developed HZO during the second month postpartum, followed by a stroke (Table 2). An arteriogram localized the occlusion in the lenticulostriate arteries, which are branches of the middle cerebral artery. Our case 8 is the only case of congenital varicella infection ever described in a pregnant woman following a bout of HZ during the 8th month of gestation(30). HZ can be accompanied by a brief maternal viremia, presumably the route of infection of the fetus(31). This newborn did not have a generalized varicella-like exanthem at time of delivery, but on day 2 of life the newborn developed a zosteriform rash on the scalp in the distribution of the right ophthalmic branch of the trigeminal ganglion. The lesion disappeared after initiation of therapy with acyclovir. However, at 2 years of age, she presented again with left hemiparesis and stroke. As noted in Table 2, this infant also had detectable VZV DNA in the cerebrospinal fluid at age 2 years.

Concepts of viral pathogenesis involving the trigeminal ganglion.

The natural history and management of HZO is very well documented(32). One of the classic published cases had a complete autopsy, including electron microscopy examination(33). The case involved a patient with myeloma cancer who developed HZO of the right eye 4 days before

her death. At autopsy, the right trigeminal ganglion was removed along with the ophthalmic division of the trigeminal nerve and a portion of the skin with the vesicular lesions. When examined by light microscopy, sections of the trigeminal ganglion showed severe degeneration with disarray of the satellite cells. When examined by electron microscopy, numerous larger mature VZV particles were observed within vacuoles in the cytoplasm. VZV particles were also observed in the electron micrographs of the satellite cells withing the trigeminal ganglion. Similarly, viral particles were detected in the skin with the herpes zoster rash. The viral particles seen at autopsy would closely resemble those shown in Figure 1.

During varicella in childhood, virus is carried retrograde from the skin vesicles on the face via sensory fibers to the trigeminal ganglion (Figure 2). After reactivation in the trigeminal ganglion, the virus travels via afferents to the cerebral arteries. Our primary source of information about the trigeminal ganglion and innervation of the cervical arteries was generated in animal studies(34-36). In one experiment, neurosurgery was carried out on adult cynomolgus monkeys in order to induce Wallerian degeneration of cervical artery nerves derived from the trigeminal ganglion. The results demonstrated that the anterior circle of Willis received innervation from the ophthalmic branch, and to a lesser extent from the maxillary

branch of the trigeminal ganglion(37). This innervation extends into the anterior and middle cerebral arteries and the lenticulostriate arteries.

In the 8 cases we identified, the time interval from HZO to stroke varied from a few weeks to 10 months (Table 1). The difference in intervals cannot be explained by differences in velocity of a virus within a sensory nerve. Several studies in animal nerves and a single study in the human sciatic nerve have demonstrated that VZV travels at a velocity around 5-6 mm per hour or around 13 cm in one day(38). The human study was carried out after observation of herpes zoster of the medial left foot in a 9-year-old boy with acute lymphocyte leukemia. After reactivation in the trigeminal ganglion, VZV would arrive at the middle cerebral artery within a few hours (Figure 2).

We speculate that the differences in intervals between HZO and subsequent stroke are more likely related to the number of infectious viral particles that arrive at the cerebral artery (Figure 2). That number would depend in turn on the number of sensory neurons carrying virus at one time to the artery. The larger the number of viral particles, the more rapid the cycle of inflammation in the artery and the shorter the interval after HZO. In turn, the above statement

implies that the size of the focus of reactivation within the trigeminal ganglion can vary greatly from individual to individual with stroke.

At the current time, we do not know the precise molecular event that triggers a reactivation. We do know that diseases which lower both innate and adaptive immunity are associated with an increased rate of HZ. In particular, diseases or treatment protocols that lower cellular immunity place the patient at high risk for HZ. Common diseases include the hematologic cancers and their treatment regimens(39). Chronic asthma in children is associated with an increased rate of HZ(40). Even a short regimen of oral corticosteroids, for example, a steroid burst therapy, can lead to HZ, probably secondary to the abrupt lymphocytopenia(41). Similarly, the biologic medications now prescribed to treat hematologic diseases of children increase the likelihood of HZ(42).

Viral pathogenesis involving the superior cervical ganglion.

The above section provides an outline for stroke following VZV reactivation in the trigeminal ganglion. A similar mode of pathogenesis is also likely for VZV reactivation in the superior cervical ganglion (Figure 2). Autopsy studies of the ganglia of the human head and neck have

found latent VZV in the superior cervical ganglia(43). Within the arterial extensions from the Circle of Willis, the anterior circulation arteries are preferentially innervated by the trigeminal ganglion with less sympathetic presence. The basilar artery, on the other hand, is innervated by more fibers from the superior cervical ganglion than the trigeminal ganglion(44). Based on these observations of anterograde and retrograde neuronal tracing in a rat brain (45), VZV reactivation in the superior cervical ganglion could be an explanation for basilar artery stroke in children and adults. VZV particles have also been observed in the basilar artery(46).

Stroke after varicella versus stroke after HZ in children

The mechanism by which childhood varicella (chickenpox) leads to subsequent pediatric stroke is not as well delineated. A viremia is a prominent feature of every varicella infection and leads to the characteristic vesicular exanthem, as virus exits the capillaries and enters the epidermis to undergo several cycles of replication(47, 48). Therefore, many stroke investigators have assumed that the virus is carried into the brain and its arteries at the same time. But that hypothesis does not fit well with the fact that the vast majority of strokes are unilateral and occur in the territories of just two arteries, the middle cerebral and the anterior cerebral artery.

Instead we propose a new hypothesis based on data acquired from animal experiments with pseudorabies virus (PRV)(49). PRV is the herpesvirus of swine; it is closely related to VZV at a genomic level. In the model for VZV latency (Figure 2), virus is carried from the skin vesicles to the trigeminal ganglion where the virus enters latency for years, without undergoing further rounds of replication. However, PRV exhibits other expanded properties. Under certain conditions, PRV will continue to replicate in a sensory ganglion after arrival during a primary PRV infection(50). In turn, that newly assembled virus can be carried anterograde from the sensory ganglion to other innervated sites without any interval for latency. This pattern of transit through PRV neurons is called the PRV round trip model. Because there are no good animal models for VZV, this experiment cannot be repeated with VZV rather PRV.

We propose that in a limited number of cases of varicella in children, a similar round-trip model of infection occurs. After virus is carried to the trigeminal ganglion, rather than entering latency, another cycle of replication occurs, after which virus is carried to the cerebral arteries unilaterally. The above hypothesis could explain why stroke following varicella occurs in the same arterial distributions as stroke following HZ.

Concluding comments

Viral infections in children have been strongly associated with acute ischemic stroke(51-53). Our review complements a review of stroke in Canadian children published 20 years ago(1). In a cohort study of 70 consecutive children with acute ischemic stroke, they observed that 31% (22 cases) had a history of varicella in the year preceding the stroke. (This study was carried out before universal varicella vaccination in Canada.) They estimated that the absolute risk of stroke was one case in every 15,000 children with varicella. Moreover, they did propose that the most likely mode of pathogenesis was transfer of virus from the trigeminal ganglion to the cerebral arteries.

After initiation of universal varicella vaccination in countries such as the United States, the usual complications after varicella have dropped precipitously followed by a sharp decrease in hospitalizations, yet childhood arterial ischemic stroke continues to occur. Even in countries with universal varicella immunization programs, there may still be a reservoir of unimmunized children who acquire wild-type varicella infections and therefore are candidates for FCA. Some immunized children can contract a break-through infection with wild-type varicella.

Furthermore, the case of stroke in a 2-year old who had an intrauterine varicella infection after maternal herpes zoster is an important addition to the childhood stroke literature (30). Before this well documented case report in 2006, there was no recognition that a pregnant woman with herpes zoster could transmit the viral infection to her fetus. The annual incidence of herpes zoster in women of child-bearing age is around 2 per 1000 person years.

Another hypothesis is that other herpes viruses can initiate a similar pattern of inflammation in the cerebral arteries. One possibility is herpes simplex virus type 1 (HSV-1), a virus closely related to VZV. Acute infections with HSV have been associated with stroke(51, 54). Yet, HSV-1 reactivations are common in many children; thus the question is raised whether HSV reactivation has a pathological role in stroke or is a response to stroke. Further studies to assess the roles of HSV and VZV in stroke are being carried out as part of the virological studies in a prospective cohort study (Vascular effects of Infection in Pediatric Stroke; VIPS II) (53). A better understanding of this complex relationship between viruses and childhood stroke may lead to new therapeutic options for stroke prevention.

Acknowledgments. C.S. was a summer undergraduate research assistant at the University of Iowa from Concordia College, Moorhead, MN.

Funding. Research by CG was funded by NIH grant AI 153817: HJF was funded by NIH grant NS104094.

Author contributions. Conceptualization: C.G. and H.J.F; original draft preparation: C.S. and C.G.; preparation of tables and figures: C.S. and C.G.; final editing of manuscript: C.G. and H.J.F. All authors have read and agreed to the current version of manuscript.

Conflicts of interests. The authors have no conflicts of interest to report.

References.

1. Askalan R, Laughlin S, Mayank S, Chan A, MacGregor D, Andrew M, et al. Chickenpox and stroke in childhood: a study of frequency and causation. Stroke. 2001;32(6):1257-62.

2. Grose C, Shaban A, Fullerton HJ. Common Features Between Stroke Following Varicella in Children and Stroke Following Herpes Zoster in Adults : Varicella-Zoster Virus in Trigeminal Ganglion. Curr Top Microbiol Immunol. 2023;438:247-72.

3. Weller TH. Varicella and herpes zoster. Changing concepts of the natural history, control, and importance of a not-so-benign virus. N Engl J Med. 1983;309(23):1434-40.

4. Davison AJ, Scott JE. The complete DNA sequence of varicella-zoster virus. J Gen Virol. 1986;67 (Pt 9)(Pt 9):1759-816.

5. Grose C. Pangaea and the Out-of-Africa Model of Varicella-Zoster Virus Evolution and Phylogeography. J Virol. 2012;86(18):9558-65.

6. McGeoch DJ, Davison AJ. The molecular evolutionary history of the herpesviruses. In: Domingo E, Webster R, Holland J, editors. Origin and evolution of viruses. New York: Academic Press; 1999. p. 441-65.

7. Hope-Simpson RE. The Nature of Herpes Zoster: A Long-Term Study and a New Hypothesis. Proc R Soc Med. 1965;58:9-20.

8. Gershon AA, Arvin AM, Levin MJ, Seward JF, Schmid DS. Varicella vaccine in the United States: a decade of prevention and the way forward. J Infect Dis. 2008;197 Suppl 2:S39-40.

9. Harpaz R, Leung JW. The Epidemiology of Herpes Zoster in the United States During the Era of Varicella and Herpes Zoster Vaccines: Changing Patterns Among Children. Clin Infect Dis. 2019;69(2):345-7.

10. Moodley A, Swanson J, Grose C, Bonthius DJ. Severe Herpes Zoster Following Varicella Vaccination in Immunocompetent Young Children. J Child Neurol. 2019;34(4):184-8.

11. McCarthy KN, C OM, Butler KM, Gavin PJ. Varicella Related Hospital Admissions in Ireland. Ir Med J. 2019;112(7):966.

12. Goh AEN, Choi EH, Chokephaibulkit K, Choudhury J, Kuter B, Lee PI, et al. Burden of varicella in the Asia-Pacific region: a systematic literature review. Expert Rev Vaccines. 2019;18(5):475-93.

13. Hung PY, Lee WT, Shen YZ. Acute hemiplegia associated with herpes zoster infection in children: report of one case. Pediatr Neurol. 2000;23(4):345-8.

14. Francois P, Bost C, Pavese P, Bost M. Herpes zoster ophthalmicus with delayed contralateral hemiplegia. Pediatr Infect Dis J. 1996;15(5):471-2.

15. Burbaud P, Berge J, Lagueny A, Mensire A, Melon M, Caille JM, et al. Delayed-onset hemidystonia secondary to herpes zoster ophthalmicus-related intracerebral arteritis in an adolescent. J Neurol. 1997;244(7):470-2.

16. Walker RJ, 3rd, el-Gammal T, Allen MB, Jr. Cranial arteritis associated with herpes zoster. Case report with angiographic findings. Radiology. 1973;107(1):109-10.

17. Moriuchi H, Rodriguez W. Role of varicella-zoster virus in stroke syndromes. Pediatr Infect Dis J. 2000;19(7):648-53.

18. Cadavid D, Pearl PL, Dubovsky EC, Angiolillo A, Vezina LG. Stroke after zoster ophthalmicus in a 12-year-old girl with protein C deficiency. Neurology. 1999;53(5):1128-9.

19. Leis AA, Butler IJ. Infantile herpes zoster ophthalmicus and acute hemiparesis following intrauterine chickenpox. Neurology. 1987;37(9):1537-8.

20. Grose C. Metagenomic sequencing of cerebrospinal fluid from children with meningitis. EBioMedicine. 2022;84:104287.

21. Laforet EG, Lynch CL, Jr. Multiple congenital defects following maternal varicella; report of a case. N Engl J Med. 1947;236(15):534-7.

22. Savage MO, Moosa A, Gordon RR. Maternal varicella infection as a cause of fetal malformations. Lancet. 1973;1(7799):352-4.

23. Williamson AP. The varicella-zoster virus in the etiology of severe congenital defects. A survey of eleven reported instances. Clin Pediatr (Phila). 1975;14(6):553-5, 8-9.

24. Srabstein JC, Morris N, Larke RP, DeSa DJ, Castelino BB, Sum E. Is there a congenital varicella syndrome? J Pediatr. 1974;84(2):239-43.

25. Cuthbertson G, Weiner CP, Giller RH, Grose C. Prenatal diagnosis of second-trimester congenital varicella syndrome by virus-specific immunoglobulin M. J Pediatr. 1987;111(4):592-5.

26. Bai PV, John TJ. Congenital skin ulcers following varicella in late pregnancy. J Pediatr. 1979;94(1):65-7.

27. Grose C, Itani O. Pathogenesis of congenital infection with three diverse viruses: varicella-zoster virus, human parvovirus, and human immunodeficiency virus. Semin Perinatol. 1989;13(4):278-93.

28. Enders G, Miller E, Cradock-Watson J, Bolley I, Ridehalgh M. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. Lancet. 1994;343(8912):1548-51.

29. Grose C. Congenital varicella-zoster virus infection and the failure to establish virus-specific cell-mediated immunity. Mol Biol Med. 1989;6(5):453-62.

30. West SL, Newton RW, Baildam EM, Turner AJ, Arkwright PD. Recurrent hemiplegia associated with cerebral vasculopathy following third trimester maternal herpes zoster infection. Dev Med Child Neurol. 2006;48(12):991-3.

31. Satyaprakash AK, Tremaine AM, Stelter AA, Creed R, Ravanfar P, Mendoza N, et al. Viremia in acute herpes zoster. J Infect Dis. 2009;200(1):26-32.

32. Liesegang TJ. Diagnosis and therapy of herpes zoster ophthalmicus. Ophthalmology. 1991;98(8):1216-29.

33. Esiri MM, Tomlinson AH. Herpes Zoster. Demonstration of virus in trigeminal nerve and ganglion by immunofluorescence and electron microscopy. J Neurol Sci. 1972;15(1):35-48.

34. Mayberg MR, Zervas NT, Moskowitz MA. Trigeminal projections to supratentorial pial and dural blood vessels in cats demonstrated by horseradish peroxidase histochemistry. J Comp Neurol. 1984;223(1):46-56.

35. Liu-Chen LY, Han DH, Moskowitz MA. Pia arachnoid contains substance P originating from trigeminal neurons. Neuroscience. 1983;9(4):803-8.

36. Ruskell GL, Simons T. Trigeminal nerve pathways to the cerebral arteries in monkeys. J Anat. 1987;155:23-37.

37. Simons T, Ruskell GL. Distribution and termination of trigeminal nerves to the cerebral arteries in monkeys. J Anat. 1988;159:57-71.

38. Tannous R, Grose C. Calculation of the anterograde velocity of varicella-zoster virions in a human sciatic nerve during shingles. J Infect Dis. 2011;203(3):324-6.

39. Good RA, Smith RT, Vernier RL. Serious untoward reactions to therapy with cortisone and adrenocorticotropin in pediatric practice. II. Pediatrics. 1957;19(2):272-84.

40. Kim BS, Mehra S, Yawn B, Grose C, Tarrell R, Lahr B, et al. Increased risk of herpes zoster in children with asthma: a population-based case-control study. J Pediatr. 2013;163(3):816-21.

41. Price NB, Grose C. Corticosteroids Contribute to Serious Adverse Events Following Live Attenuated Varicella Vaccination and Live Attenuated Zoster Vaccination. Vaccines (Basel). 2021;9(1).

42. Pappas DA, Hooper MM, Kremer JM, Reed G, Shan Y, Wenkert D, et al. Herpes Zoster Reactivation in Patients With Rheumatoid Arthritis: Analysis of Disease Characteristics and Disease-Modifying Antirheumatic Drugs. Arthritis Care Res (Hoboken). 2015;67(12):1671-8.

43. Richter ER, Dias JK, Gilbert JE, 2nd, Atherton SS. Distribution of herpes simplex virus type 1 and varicella zoster virus in ganglia of the human head and neck. J Infect Dis. 2009;200(12):1901-6.

44. Keller JT, Beduk A, Saunders MC. Origin of fibers innervating the basilar artery of the cat. Neurosci Lett. 1985;58(2):263-8.

45. Arbab MA, Wiklund L, Svendgaard NA. Origin and distribution of cerebral vascular innervation from superior cervical, trigeminal and spinal ganglia investigated with retrograde and anterograde WGA-HRP tracing in the rat. Neuroscience. 1986;19(3):695-708.

46. Fukumoto S, Kinjo M, Hokamura K, Tanaka K. Subarachnoid hemorrhage and granulomatous angiitis of the basilar artery: demonstration of the varicella-zoster-virus in the basilar artery lesions. Stroke. 1986;17(5):1024-8.

47. Grose C. Variation on a theme by Fenner: the pathogenesis of chickenpox. Pediatrics. 1981;68(5):735-7.

48. Asano Y, Itakura N, Kajita Y, Suga S, Yoshikawa T, Yazaki T, et al. Severity of viremia and clinical findings in children with varicella. J Infect Dis. 1990;161(6):1095-8.

49. Grose C, Enquist LW. The round trip model for severe herpes zoster caused by live attenuated varicella vaccine virus. J Med Virol. 2020;92(8):938-40.

50. Granstedt AE, Brunton BW, Enquist LW. Imaging the transport dynamics of single alphaherpesvirus particles in intact peripheral nervous system explants from infected mice. mBio. 2013;4(3):e00358-13.

51. Elkind MS, Hills NK, Glaser CA, Lo WD, Amlie-Lefond C, Dlamini N, et al. Herpesvirus Infections and Childhood Arterial Ischemic Stroke: Results of the VIPS Study. Circulation. 2016;133(8):732-41.

52. Fullerton HJ, Luna JM, Wintermark M, Hills NK, Tokarz R, Li Y, et al. Parvovirus B19 Infection in Children With Arterial Ischemic Stroke. Stroke. 2017;48(10):2875-7.

53. Cornet MC, Grose C, Vexler Z, Wu YW, Fullerton HJ. The Role of Infection and Inflammation in the Pathogenesis of Pediatric Arterial Ischemic Stroke. Semin Pediatr Neurol. 2022;44:100995.

54. Terlizzi V, Improta F, Di Fraia T, Sanguigno E, D'Amico A, Buono S, et al. Primary herpes virus infection and ischemic stroke in childhood: a new association? J Clin Neurosci. 2014;21(9):1656-8.

Legends.

Figure 1. Electron micrograph of cells infected with varicella-zoster virus. A complete virion is 200 nanometers in diameter. Several viral particles are visible. Abbreviations: E, envelope; T, tegument; C. capsid; G, genome.

Figure 2. Diagrammatic representation of the life cycle of varicella-zoster virus and stroke. A. Route to the cerebral arteries. Virus is carried in nociceptive fibers from the skin vesicles of the upper face to the trigeminal ganglion, where the virus enters latency. After several years, the virus reactivates as herpes zoster; when reactivation occurs in the trigeminal ganglion, viral particles may travel to the tissues around the eye, to cause HZO. Some particles may travel to the middle and anterior cerebral arteries via the anterior Circle of Willis. Inflammation leads to stroke. B. Child with varicella. The average case of varicella includes an exanthem with around 150 vesicles. The skin vesicles containing live virus first form at the hairline and upper face. Therefore, virus is usually carried to the trigeminal ganglion, since this ganglion supplies sensory fibers to the face. C. Alternative route to the cerebral arteries. Some virus is carried from the superior cervical ganglion to the caudal Circle of Willis and eventually to the basilar artery.