



Central nervous system infections produced by varicella zoster virus

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Purpose of review

Varicella zoster virus (VZV) causes varicella, establishes latency, then reactivates to produce herpes zoster. VZV reactivation can also cause central nervous system (CNS) disease with or without rash. Herein, we review these CNS diseases, pathogenesis, diagnosis, and treatment.

Recent findings

The most common CNS manifestation of VZV infection is vasculopathy that presents as headache, cognitive decline, and/or focal neurological deficits. VZV vasculopathy has also been associated with cerebral amyloid angiopathy and moyamoya syndrome. Rarely, VZV will produce a meningitis, encephalitis, cerebellitis, and myelopathy. Pathogenic mechanisms include direct VZV infection of affected tissue, persistent inflammation, and/or virus-induced hypercoagulability. Diagnosis is confirmed by the temporal association of rash to disease onset, intrathecal synthesis of anti-VZV antibodies, and/or the presence of VZV DNA in CSF. Most cases respond to intravenous acyclovir with corticosteroids.

Summary

VZV produces a wide spectrum of CNS disorders that may be missed as some cases do not have an associated rash or a CSF pleocytosis. Clinicians must be vigilant in including VZV in their differential diagnosis of CNS infections as VZV is a ubiquitous pathogen; importantly, VZV CNS infections are treatable with intravenous acyclovir therapy and corticosteroids.

Keywords

cerebellitis, encephalitis, myelopathy, varicella zoster virus, vasculopathy

INTRODUCTION

Varicella zoster virus (VZV) is a ubiquitous, exclusively human alphaherpesvirus. Primary infection causes varicella (chickenpox), after which VZV establishes latency in ganglionic neurons and adrenal glands [1–5]. With a decline in VZV-specific cell-mediated immunity, as seen in elderly or immunosuppressed individuals, VZV reactivates to produce zoster that can be complicated by postherpetic neuralgia, zoster sine herpete, and other multisystem disorders (Fig. 1) [6]. VZV has also been associated with giant cell arteritis and aortitis [7,8]. Aside from these peripheral diseases, VZV can also spread centrally to produce vasculopathy, meningitis, encephalitis, cerebellitis, and myelopathy with or without rash. The burden of VZV disease is significant, given that more than 90% of the world population harbors latent virus and more than 50% will reactivate by 85 years of age and develop disease. Herein, we review the clinical features, pathogenesis, diagnosis, and treatment of VZV central nervous system (CNS) disorders.

VARICELLA ZOSTER VIRUS VASCULOPATHY

VZV vasculopathy manifests as stroke, aneurysm, dissection, and other vascular abnormalities. Patients present with headache, confusion, hemiparesis, and/or other focal neurological deficits. VZV vasculopathy can be acute and monophasic or chronic/progressive. In these chronic/progressive cases, aside from VZV vasculopathy causing a step-wise accumulation of neurological deficits [9], recent reports have described VZV vasculopathy causing a multiinfarct dementia over a 2-year period in a 69-year-old man without associated rash [10]

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KEY POINTS

- As tissues and most arteries are innervated, VZV can directly infect them following reactivation from ganglia and spread along neurites, producing a wide spectrum of disease.
- VZV CNS infections can manifest as a vasculopathy, meningitis, encephalitis, cerebellitis, and myelopathy, with or without varicella or zoster rash.
- VZV CNS disease can be diagnosed by temporal association of rash and symptoms/signs, intrathecal synthesis of anti-VZV antibodies, and/or the presence of VZV DNA in CSF.
- VZV CNS disease is treatable with intravenous acyclovir and corticosteroids, as well as anticoagulants if a hypercoagulable state exists.

and moyamoya syndrome over an 11-month period in a 10-year old girl with varicella [11[■]].

Stroke

Multiple epidemiological studies have shown an increased risk of transient ischemic attacks (TIAs) and stroke after zoster compared with nonzoster controls (reviewed in ref. [12[■]]). Specifically, a retrospective US study shows that the adjusted incident rate ratios (IRRs) for TIAs are 1.56 or 5.12 for all zoster patients or patients aged 18–49 years, respectively; the IRRs for stroke are 1.40 and 8.12 for all

zoster patients or patients aged 18–49 years, respectively [13].

An analysis of 30 VZV vasculopathy cases shows that 63% had rash, 67% had a CSF pleocytosis, 97% had brain imaging abnormalities, and 70% had angiographic abnormalities [14]. Detection of anti-VZV IgG antibody was the best test for diagnosis as 93% of the individuals had intrathecal synthesis of anti-VZV antibodies and only 30% had VZV DNA in CSF [15]. Approximately 67% of individuals stabilized/improved with antiviral therapy. Because rash is absent in 37% of individuals VZV DNA is absent in 70% of CSF, and there is an average delay of 4.2 months from time of rash to stroke symptoms/signs, the diagnosis of VZV vasculopathy is often missed. Another study of four patients showed that all had rash and stroke involving the anterior and/or posterior circulation; three had elevated hypercoagulable factors; two had cranial nerve palsies preceding stroke; one had angiographic abnormalities; and three responded to acyclovir, steroids, and antithrombotic agents [16].

Aneurysm and pseudoaneurysm

VZV vasculopathy can present as cerebral aneurysm, with or without hemorrhage or rash [17–19]. Evidence that VZV infection of arteries is directly involved in pathogenesis is provided by two cases showing that the aneurysmal wall contained viral antigen and herpesvirus particles [20,21]. A noteworthy case is that of an immunosuppressed 41-

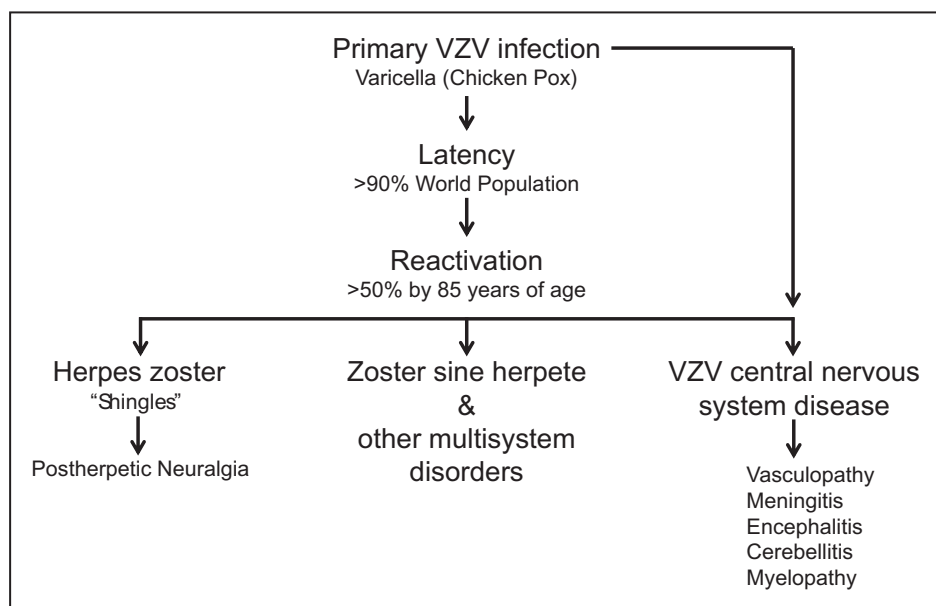


FIGURE 1. Varicella zoster virus produces varicella on primary infection, establishes latency, then reactivates to cause zoster that can be complicated by postherpetic neuralgia, zoster sine herpete, and a spectrum of central nervous system disease. VZV, varicella zoster virus.

year-old woman who developed disseminated zoster and a severe headache in the setting of a normal angiogram, followed by headache recurrence and development of nine new intracranial aneurysms [22]. Diagnosis was made by the presence of VZV DNA in CSF; as acyclovir treatment led to clinical improvement and size reduction/resolution of the vascular lesions – these lesions initially coined as ‘aneurysms’, most likely represented pseudoaneurysms.

Dissection and other vascular abnormalities

Rare cases of VZV vasculopathy manifesting as dissections have been described. Two pediatric cases developed rash followed 2–4 weeks later by carotid artery dissections in the setting of vigorous activity [23]. Although trauma and exercise are frequently associated with arterial dissection, VZV infection in the wall of an artery may predispose the artery to dissection if it is subjected to further trauma. Another case describes a 60-year-old woman with zoster and a ruptured left vertebral artery dissection and subarachnoid hemorrhage; anti-VZV antibodies were present in CSF; and patient recovered after coil embolization, intravenous acyclovir, and antiplatelet therapy [24]. A final noteworthy report describes a 62-year-old man with herpes zoster ophthalmicus who developed headache and vomiting 1 month later; MRI revealed an acute infarct of the frontal lobe and bilateral internal carotid artery dissection. Patient stabilized with antiviral therapy, corticosteroids, and heparin [25].

Other rare vascular abnormalities have been associated with VZV vasculopathy, including dolichoectasia of the anterior and posterior circulation with multiple small deep-seated infarcts in a late adult cancer survivor [26], ectasia with stenosis and aneurysm in AIDS patients [17], and sinus thrombosis in adult and pediatric patients [27–32].

Pathogenesis of varicella zoster virus vasculopathy

Direct virus infection, persistent inflammation and virus-induced hypercoagulability may contribute independently or together in VZV vasculopathy pathogenesis.

In latently infected individuals, VZV vasculopathy occurs after virus reactivates from trigeminal or upper cervical ganglia then travels along neurites to infect the adventitia of cerebral arteries; a similar process can occur during primary infection. Infected adventitial fibroblasts secrete cytokines that recruit inflammatory cells to the arterial wall; soluble factors released by immune cells contribute to

accumulation of intimal myofibroblasts, potentially leading to ischemia, as well as destruction of the media, potentially leading to aneurysm, pseudoaneurysm, and other arterial abnormalities [reviewed in refs. [33,34–37]. A recent study found that adventitial fibroblasts may transdifferentiate into myofibroblasts during infection and cause endothelial cell activation, in part through apoptotic virion-containing microparticles [38[¶]]. In addition, VZV may produce a hypercoagulable state, leading to thrombosis [39,40]. Finally, with regards to recurrent or persistent VZV vasculopathy, this may be produced by intermittent episodes of reactivation and virus deposition to the arteries; virus-induced epigenetic alterations of adventitial fibroblasts such that they chronically secrete pro-inflammatory cytokines; and/or deposition of insoluble, toxic, proinflammatory amyloid, as supported by recent studies showing the co-existence of VZV vasculopathy with cerebral amyloid angiopathy [41[¶]], production of intracellular amyloid-beta and amyloid, as well as production of an extracellular amyloidogenic environment in VZV-infected cells *in vitro* [42], and elevated levels of amyloid and an amyloidogenic environment in acute zoster plasma [43].

VARICELLA ZOSTER VIRUS MENINGITIS AND ENCEPHALITIS

VZV infection can produce a meningitis [44] or encephalitis [45] that can co-exist together [46–49], as well as occur in conjunction with a VZV vasculopathy and/or radiculitis [50,51,52^{¶¶}]. A nationwide prospective cohort study in Denmark of 92 adults with VZV encephalitis identified key features: there was a near equal gender distribution with a median age of 75 years; the incidence was 5.3/1 000 000/year; 39% were immunocompromised; and symptoms included confusion (76%), headache (56%), nausea (45%), gait abnormalities (42%), and personality change (41%) [52^{¶¶}]. Imaging showed vasculitis in 16% and encephalitic abnormalities in 13% with a predilection for the brainstem and deep brain structures. Patients were treated with intravenous acyclovir, and in-hospital, 1-month, and 3-month mortalities were 4, 9, and 11%, respectively. Unfavorable outcomes were present in 69%.

VARICELLA ZOSTER VIRUS CEREBELLITIS

Cerebellitis is another rare CNS complication of VZV infection that can occur before, during or after rash, as well as in the absence of rash [53–55]. Patients with VZV cerebellitis present with balance problems, speech disturbances, nystagmus, headache, and vomiting. The mechanisms of VZV cerebellitis

is unclear and may involve postviral inflammatory responses or direct infection of cerebellum [53,54].

VARICELLA ZOSTER VIRUS MYELOPATHY

VZV myelopathy patients typically present with a spastic paraparesis, with or without sensory features or sphincter problems; MRI may show a transverse myelitis or longitudinal serpiginous-enhancing lesions [56,57]. In a study of 31 cases of VZV myelitis, 54.8% were immunocompromised (predominantly with acquired immunodeficiency syndrome); 45.2% had a preceding rash at the level of myelopathy; and with antiviral therapy, immunocompetent patients had favorable outcomes but immunocompromised patients had poor outcomes yet reduced mortality [58²²]. Postmortem analyses of the spinal cord may show frank invasion of VZV in the parenchyma with associated inflammation [57] and, in some instances, spread of virus to adjacent nerve roots. VZV can also produce spinal cord infarction [59].

DIAGNOSIS AND TREATMENT

Diagnosis and treatment for VZV CNS infections follow those for VZV vasculopathy, where more studies have been published [14,15]. Overall, diagnosis is made by: the temporal association of rash to onset of neurological symptoms and signs; the presence of VZV DNA in CSF by PCR; and intrathecal synthesis of anti-VZV antibodies. Although there are no studies on the diagnostic benefits of peripheral anti-VZV antibody levels for CNS infection, serum anti-VZV IgG and IgM can be measured; a four-fold increase in anti-VZV IgG titers indicates persistent virus infection and a positive anti-VZV IgM indicates recent infection/reactivation. Treatment includes intravenous acyclovir (10–15 mg/kg) every 8 h for 14 days, adjusted for creatinine clearance; prednisone 60 mg daily for days 1–5 of acyclovir treatment; and anticoagulants if hypercoagulability is suspected. For recurrences, an additional round of intravenous acyclovir for 14 days may be required. On the basis of our clinical experience, if the patient continues to have disabling, recurrent VZV CNS infections when intravenous acyclovir is discontinued, we evaluate for cancer that may produce global immunosuppression, as well as conduct a full immunological work-up (including natural killer cell function assays and lymphocyte proliferation/ELISPOT assays for VZV). We have observed cases of recurrence because of low immune cell or antibody subsets, natural killer cell dysfunction, and specific lymphocyte proliferation defects to VZV. For patients with confirmed immunological deficits and continued recurrence, after

intravenous acyclovir is discontinued, we continue oral valacyclovir (1 g daily) and do a trial of monthly IVIG for 6 months.

VACCINATION FOR VARICELLA ZOSTER VIRUS CENTRAL NERVOUS SYSTEM DISEASE

Currently, we have vaccines for varicella (Varivax, Merck, Kenilworth, NJ) and zoster (Zostavax, Merck; Shingrix, GlaxoSmithKlein, Philadelphia, PA). Zostavax is a live, attenuated, single-dose vaccine that prevents zoster and subsequent PHN [60]. Shingrix is the second Food and drug Administration (FDA)-approved zoster vaccine that is now the preferred vaccine recommended by the Centers for Disease Control Prevention [61,62]. Shingrix is a two-dose, nonlive, recombinant zoster vaccine containing VZV glycoprotein E and the AS01B adjuvant system. Shingrix is recommended for individuals at least 50 years of age, excluding individuals who are negative for VZV immunity, have active zoster or recurrent zoster/inflammation in the eye, or are pregnant/breastfeeding.

Although Zostavax and Shingrix prevent zoster and PHN, it is unclear if they will prevent VZV CNS disease. One study using administrative claims data of older US Medicare beneficiaries showed no associated protective effect of Zostavax on preventing acute cardiovascular events [63]; another study using self-reporting health information in a US telephone survey showed a 50% reduction in reports of stroke in vaccinated individuals compared with unvaccinated controls [64²³]. It remains to be determined if zoster vaccination is effective or potentially detrimental in VZV CNS disease. In the majority of VZV CNS disease, it is the virus-induced inflammation that causes damage, raising the possibility that a robust, vaccine-driven, immune response within cerebral arteries, brain parenchyma, or spinal cord could worsen outcomes. Alternatively, if immune-mediated clearance of VZV occurs prior to the initiation of an aberrant inflammatory response, zoster vaccination may be appropriate. Overall, although zoster vaccination prevents zoster and PHN, its efficacy for other VZV-related diseases is unknown. In addition, it is not applicable to VZV disease occurring before 50 years of age, a period when 32% of zoster cases and its complications occur [65].

Finally, the effectiveness of Varivax in preventing VZV CNS disease is also unclear. A retrospective population-based cohort study of 368 992 children found no evidence of increased stroke following vaccination [66²⁴]. However, in a 6-year-old boy who developed widespread stenosis and infarction, vaccine strain DNA was found in his CSF indicating

that reactivation of the live attenuated vaccine produced VZV vasculopathy [67]. Subsequent studies showed that he had a DOCK8 deficiency that enhanced his susceptibility to viral infection. This case illustrates that in rare cases of immunodeficiency in children, Varivax may produce CNS complications.

CONCLUSION

VZV infection of the CNS can cause vasculopathy, meningitis, encephalitis, cerebellitis, and myelopathy. Importantly, all of these VZV CNS diseases can occur without rash or months after rash, such that diagnosis is missed. Given that the majority of the population is latently infected with VZV and more than 50% will reactivate by 85 years of age, clinicians should include VZV infection in their differential diagnosis for CNS disease and perform diagnostic tests as the majority of cases are treatable with intravenous acyclovir therapy and corticosteroids.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Mahalingam R, Wellish M, Wolf W, *et al.* Latent varicella-zoster viral DNA in human trigeminal and thoracic ganglia. *N Engl J Med* 1990; 323:627–631.
2. Kennedy PG, Grinfeld E, Gow JW. Latent varicella-zoster virus in human dorsal root ganglia. *Virology* 1999; 258:451–454.
3. 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; 200:1901–1906.
4. Badani H, White T, Schulick N, *et al.* Frequency of varicella zoster virus DNA in human adrenal glands. *J Neurovirol* 2016; 22:400–402.
5. Gershon M, Gershon A. Varicella-zoster virus and the enteric nervous system. *J Infect Dis* 2018; 218(Suppl 2):S113–S119.
6. Drago F, Herzum A, Ciccicarese G, *et al.* Acute pain and postherpetic neuralgia related to Varicella zoster virus reactivation: comparison between typical herpes zoster and zoster sine herpette. *J Med Virol* 2019; 91:287–295.
7. Nagel MA, White T, Khmeleva N, *et al.* Analysis of varicella-zoster virus in temporal arteries biopsy positive and negative for giant cell arteritis. *JAMA Neurol* 2015; 11:1281–1288.
8. Gilden D, White T, Boyer PJ, *et al.* Varicella zoster virus infection in granulomatous arteritis of the aorta. *J Infect Dis* 2016; 12:1866–1871.
9. Lin CF, Hong CT, Lee WH, *et al.* Disseminated cutaneous herpes zoster and multiple cerebral infarcts in an adult with diabetes mellitus. *J Neurovirol* 2020; 26:130–132.
10. Silver B, Nagel MA, Mahalingam R, *et al.* Varicella zoster vasculopathy: a treatable form of rapidly progressive multi-infarct dementia after 2 years' duration. *J Neurol Sci* 2012; 323:245–247.

11. Kumar S, Pillai SV. Moyamoya syndrome as a manifestation of varicella-associated cerebral vasculopathy – case report and review of literature. *Childs Nerv Syst* 2019; 35:601–606.

This report reviews literature on VZV vasculopathy co-existing with moyamoya syndrome.

12. Wu PH, Chuang YS, Lin YT. Does herpes zoster increase the risk of stroke and myocardial infarction? A comprehensive review. *J Clin Med* 2019; 8:pii: e547.

A review of previously published studies around the world that assess the risk of stroke and myocardial infarction after zoster.

13. Patterson BJ, Rausch DA, Irwin DE, *et al.* Analysis of vascular event risk after herpes zoster from 2007 to 2014 US insurance claims data. *Mayo Clin Proc* 2019; 94:763–775.
14. Nagel MA, Cohrs RJ, Mahalingam R, *et al.* The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology* 2008; 70:853–860.
15. Nagel MA, Forghani B, Mahalingam R, *et al.* The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. *Neurology* 2007; 68:1069–1073.
16. Hoshino T, Toi S, Toda K, *et al.* Ischemic stroke due to virologically-confirmed varicella zoster vasculopathy: a case series. *J Stroke Cerebrovasc Dis* 2019; 28:338–343.
17. de Broucker T, Verollet D, Schoindre Y, *et al.* Cerebral vasculitis with aneurysms caused by varicella-zoster virus infection during AIDS: a new clinicoangiographical syndrome. *Rev Neurol (Paris)* 2008; 164:61–71.
18. Bhayani N, Ranade P, Clark NM, McGuinn M. Varicella-zoster virus and cerebral aneurysm: case report and review of the literature. *Clin Infect Dis* 2008; 47:e1–e3.
19. Tomkins A, Babu C, Herwadkar A, *et al.* Varicella zoster virus cerebral aneurysmal vasculopathy presenting in a newly-diagnosed HIV-positive patient. *Int J STD AIDS* 2018; 29:1351–1353.
20. Fukumoto S, Kinjo M, Hokamura K, Tanaka K. Sullbarachnoid hemorrhage and granulomatous angiitis of the basilar artery: demonstration of the varicella-virus in the basilar artery lesions. *Stroke* 1986; 17:1024–1028.
21. Fulmer BB, Dillard SC, Musulman EM, *et al.* Two cases of cerebral aneurysms in HIV+ children. *Pediatr Neurosurg* 1998; 28:31–34.
22. Liberman AL, Nagel MA, Hurley MC, *et al.* Rapid development of 9 cerebral aneurysms in varicella-zoster virus vasculopathy. *Neurology* 2014; 23:2139–2141.
23. Constantinescu CS. Association of varicella-zoster virus with cervical artery dissection in 2 cases. *Arch Neurol* 2000; 57:427.
24. Lee K, Park H, Park I, Han J. Endovascular treatment using woven stents for ruptured vertebral artery dissection aneurysm induced by varicella zoster virus: case report. *Br J Neurosurg* 2016; 30:672–674.
25. Iwasa M, Mima Y, Ito A, *et al.* A case of bilateral cervical internal carotid artery dissection following herpes zoster of the trigeminal nerve. *Rinsho Shinkeigaku* 2018; 58:292–296.
26. Dalton CM, Jäger HR, Losseff NA, Greenwood RJ. Neurological picture. Varicella zoster virus and intracranial dolichoectasia in a late adult cancer survivor. *J Neurol Neurosurg Psychiatry* 2008; 79:573.
27. Chan J, Bergstrom RT, Lanza DC, Oas JG. Lateral sinus thrombosis associated with zoster sine herpette. *Am J Otolaryngol* 2004; 25:357–360.
28. Siddiqi SA, Nishat S, Kanwar D, *et al.* Cerebral venous sinus thrombosis: association with primary varicella zoster virus infection. *J Stroke Cerebrovasc Dis* 2012; 21:917.e1–917.e4.
29. Sada S, Kammineni A, Kanikannan MA, Afshan J. Cerebral sinus venous thrombosis: a rare complication of primary varicella zoster virus. *Neurol India* 2012; 60:645–646.
30. Gayathri K, Ramalingam PK, Santhakumar R, *et al.* Cerebral sinus venous thrombosis as a rare complication of primary varicella zoster virus infection. *J Assoc Physicians India* 2016; 64:74–76.
31. Imam SF, Lodhi OUH, Fatima Z, *et al.* A unique case of acute cerebral venous sinus thrombosis secondary to primary varicella zoster infection. *Cureus* 2017; 9:e1693.
32. Khan R, Yasmeen A, Pandey AK, *et al.* Cerebral venous thrombosis and acute pulmonary embolism following varicella infection. *Eur J Case Rep Intern Med* 2019; 6:001171.
33. Nagel MA, Bubak AN. Varicella zoster virus vasculopathy. *J Infect Dis* 2018; 218:S107–S113.
34. Nagel MA, Traktinskiy I, Azarkh Y, *et al.* Varicella zoster virus vasculopathy: analysis of virus-infected arteries. *Neurology* 2011; 77:364–370.
35. Nagel MA, Traktinskiy I, Stenmark KR, *et al.* Varicella zoster virus vasculopathy: immune characteristics of virus infected arteries. *Neurology* 2013; 80:62–68.
36. Jones D, Alvarez E, Selva S, *et al.* Proinflammatory cytokines and matrix metalloproteinases in CSF of patients with VZV vasculopathy. *Neurol Neuroimmunol Neuroinflamm* 2016; 3:e246.
37. Jones D, Neff CP, Palmer BE, *et al.* Varicella zoster virus-infected cerebrovascular cells produce a proinflammatory environment. *Neurol Neuroimmunol Neuroinflamm* 2017; 4:e382.
38. Eleftheriou D, Moraitis E, Hong Y, *et al.* Microparticle-mediated VZV propagation and endothelial activation: mechanism of VZV vasculopathy. *Neurology* 2020; 94:e474–480.

This study describes new mechanisms for VZV vasculopathy.

39. Peyton BD, Cutler BS, Stewart FM. Spontaneous tibial artery thrombosis associated with varicella pneumonia and free protein S deficiency. *J Vasc Surg* 1998; 27:563–567.
 40. Thomson JJ, Retter A, Hunt BJ. Novel management of post varicella purpura fulminans owing to severe acquired protein S deficiency. *Blood Coagul Fibrinolysis* 2010; 21:598–600.
 41. Takeshita J, Nomura E, Takemaru M, *et al.* Rapidly deteriorated labor intracerebral hemorrhages: possible association of varicella zoster virus-vasculopathy. *Rinsho Shinkeigaku* 2018; 58:245–248.
- This is the first report showing VZV vasculopathy coinciding with cerebral amyloid angiopathy.
42. Bubak AN, Como CN, Coughlan CM, *et al.* Varicella zoster virus infection of primary human spinal astrocytes produces intracellular amylin, amyloid-beta, and an amyloidogenic extracellular environment. *J Infect Dis* 2019; 221:1088–1097.
 43. Bubak AN, Bessler C, Como CN, *et al.* Acute zoster plasma contains elevated amyloid, correlating with Aβ42 and amylin levels, and is amyloidogenic. *J Neurovirol* 2020; 221:1088–1097.
 44. Habib AA, Gilden D, Schmid DS, Safdieh JE. Varicella zoster virus meningitis with hypoglycorrhachia in the absence of rash in an immunocompetent woman. *J Neurovirol* 2009; 15:206–208.
 45. Halling G, Giannini C, Britton JW, *et al.* Focal encephalitis following varicella-zoster virus reactivation without rash in a healthy immunized young adult. *J Infect Dis* 2014; 210:713–716.
 46. Srivastava T, Nagpal K. Herpes zoster meningoencephalitis complicated with peripheral vascular disease: an uncommon presentation of a common disease. *Scand J Infect Dis* 2014; 46:716–718.
 47. Wakida K, Sakurai T, Nishida H. Varicella zoster virus-induced meningoencephalitis complicated with orbital apex syndrome: a case report. *Brain Nerve* 2014; 66:1103–1108.
 48. Granato A, Belluzzo M, Fantini J, *et al.* SUNCT-like syndrome attributed to varicella-zoster virus meningoencephalitis. *Neurol Sci* 2015; 36:807–808.
 49. Eyal O, Flaschner M, Ben Yehuda A, Rund D. Varicella-zoster virus meningoencephalitis in a patient treated with ruxolitinib. *Am J Hematol* 2017; 92:E74–E75.
 50. Luisier V, Weber L, Fishman D, *et al.* Definition and management of varicella zoster virus-associated meningoradiculitis: a case report. *BMC Res Notes* 2016; 9:451.
 51. Shimizu R, Ohwada C, Nagao Y, *et al.* The successful treatment of a cord blood transplant recipient with varicella zoster virus meningitis, radiculitis and myelitis with foscarnet. *Intern Med* 2017; 56:353–356.
 52. Herlin LK, Hansen KS, Bodilsen J, *et al.* Varicella zoster virus encephalitis in Denmark from 2015 to 2019 A nationwide prospective cohort study. *Clin Infect Dis* 2020; pii: ciae185 [Epub ahead of print]
- This is the largest study characterizing the incidence, symptoms, imaging abnormalities and prognosis for VZV encephalitis.
53. Nussinovitch M, Prais D, Volovitz B, *et al.* Postinfectious acute cerebellar ataxia in children. *Clin Pediatr* 2003; 42:581–584.
 54. Rossi A, Martinetti C, Morana G, *et al.* Neuroimaging of infectious and inflammatory diseases of the pediatric cerebellum and brainstem. *Neuroimag Clin N Am* 2016; 26:471–478.
 55. Cross CP, English SE, Krause MA, Zalewski NL. Acute truncal ataxia in a healthy adult with varicella zoster virus cerebellitis: a case report and literature review. *J Neurol Sci* 2019; 400:186–187.
 56. Farhat N, Daoud S, Hdiji O, *et al.* Myelopathy after zoster virus infection in immunocompetent patients: a case series. *J Spinal Cord Med* 2019; 1–5.
 57. Gilden DH, Beinlich BR, Rubinstien EM, *et al.* Varicella-zoster virus myelitis: an expanding spectrum. *Neurology* 1994; 44:1818–1823.
 58. Hung CH, Chang KH, Kuo HC, *et al.* Features of varicella zoster virus myelitis and dependence on immune status. *J Neurol Sci* 2012; 318:19–24.
- This is the largest study of features and outcomes of VZV myelopathy in immunocompetent versus immunocompromised patients.
59. Orme HT, Smith AG, Nagel MA, *et al.* VZV spinal cord infarction identified by diffusion-weighted MRI (DWI). *Neurology* 2007; 69:398–400.
 60. Oxman MN, Levin MJ, Johnson GR, *et al.* A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005; 352:2271–2284.
 61. Lal H, Cunningham AL, Godeaux O, *et al.* ZOE-50/70 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 2015; 372:2087–2096.
 62. Cunningham AL, Lal H, Kovac M, *et al.* Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med* 2016; 375:1019–1032.
 63. Minassian C, Thomas SL, Smeeth L, *et al.* Acute cardiovascular events after herpes zoster: a self-controlled case series analysis in vaccinated and unvaccinated older residents of the United States. *PLoS Med* 2015; 12:e1001919.
 64. Klaric JS, Beltran TA, McClenathan BM. An association between herpes zoster vaccination and stroke reduction among elderly individuals. *Mil Med* 2019; 184(Suppl 1):126–132.
- This study reports that zoster vaccination reduces stroke risk after zoster.
65. Yawn BP, Gilden D. The global epidemiology of herpes zoster. *Neurology* 2013; 81:928–930.
 66. MacDonald SE, Dover DC, Hill MD, *et al.* Is varicella vaccination associated with pediatric arterial ischemic stroke? A population-based cohort study. *Vaccine* 2018; 36:2764–2767.
- This large retrospective study demonstrates that varicella vaccination does not increase risk for arterial ischemic stroke in children.
67. Sabry A, Hauk PJ, Jing H, *et al.* Vaccine strain varicella-zoster virus-induced central nervous system vasculopathy as the presenting feature of DOCK8 deficiency. *J Allergy Clin Immunol* 2014; 133:1225–1227.