Daniel Esau, BAppSc, MHSc, MD, Divya Virmani, MD

Multidermatomal varicella zoster with multiple cranial nerve involvement presenting with partial ophthalmoplegia in an immunocompetent woman

The case of an immunocompetent patient who presented with partial ophthalmoplegia, a rare complication of varicella-zoster virus infection, suggests that corticosteroids can be used in conjunction with antiviral medication to treat the condition in select patients.

ABSTRACT: Varicella-zoster virus (VZV) is rarely the cause of multiple cranial nerve palsies. Partial or complete ophthalmoplegia can occur with VZV infection, but the optimal treatment for this condition is unknown. We report the case of a 79-year-old immunocompetent woman who presented with multidermatomal VZV, herpes zoster ophthalmicus, multiple cranial nerve palsies, and partial unilateral ophthalmoplegia. Our report highlights the use of corticosteroids and antivirals to treat her VZV-associated partial ophthalmoplegia.

Dr Esau is a fourth-year internal medicine resident at the University of British Columbia. Dr Virmani is an infectious disease consulting physician at Royal Jubilee Hospital.

This article has been peer reviewed.

Reactivation of varicella-zoster virus (VZV) causes shingles, which most often affects a single cutaneous sensory nerve but can also involve sensory or motor cranial nerves. In rare cases, reactivated VZV can cause multiple cranial nerve palsies and partial or complete ophthalmoplegia. The optimal management of patients with this condition remains unclear.

Case data

A 79-year-old woman presented to the emergency department with left VZV ophthalmicus and partial sixth and third nerve palsies. Four weeks prior to presentation, she had developed a vesicular rash on her left forehead and face, and had begun experiencing nausea, headache, and general malaise. She was prescribed valacyclovir as treatment of herpes zoster ophthalmicus and was referred to ophthalmology.

One week prior to presentation, the patient was seen by ophthalmology and was noted to have herpes zoster–related anterior uveitis with suspected vitreous spillover. Extraocular muscle function showed no abnormalities. Due to the patient's ongoing gastrointestinal intolerance of valacyclovir, her prescription was switched to acyclovir. On follow-up 1 week later, she had developed a 5-day history of horizontal diplopia and photophobia. Her vital signs showed no abnormalities. Periorbital swelling and ptosis were noted in the left eye, along with a partial sixth nerve palsy with severe limitation in eye abduction. Her left eye was midline in the neutral position. The right

Key points

- Varicella zoster can affect both sensory and motor cranial nerves, and is a rare cause of complete or partial ophthalmoplegia in both immunocompromised and immunocompetent patients.
- The underlying mechanism of cranial nerve involvement is unknown but may involve direct viral infection and postinfectious inflammation of the cranial nerves.
- There is little evidence to guide treatment of varicella-zoster virus ophthalmoplegia, but the use of corticosteroids in addition to antivirals may target inflammation involved in the pathogenesis of this condition.

pupil was 3 mm and responsive; the left was 6 mm and had a sluggish and painful response to light. Her corneal reflexes were intact. A crusted macular exanthem was present over the left V1 dermatome and on the right back and breast (T4 dermatome). Cardiopulmonary and abdominal exams revealed no abnormalities. The patient had no meningismus. Anterior uveitis had improved, and visual acuity was 20/20 OU with correction. She was referred to the emergency department for suspected neurologic involvement of VZV.

The patient's medical history included bilateral hip replacements, osteoporosis, pseudophakia OU, glaucoma, anterior ischemic optic neuropathy in the left eye 13 years prior, and remote Graves' disease with radioiodine ablation. A lumbar puncture was performed, and the patient was admitted to hospital for intravenous acyclovir. Varicella zoster, herpes simplex, and enterovirus polymerase chain reaction (PCR) were negative in the cerebrospinal fluid (CSF). Gram stain and culture of the CSF were negative. Cell count of the CSF revealed 3×10^6 RBC per litre and 33×10^6 nucleated cells per litre, 91% of which were lymphocytes. Complete blood count, electrolytes, and creatinine showed no abnormalities. An HIV screen was negative. IgG, IgA, and IgM levels, and CD4, CD8, and complement levels showed no abnormalities. A CT scan of her chest, abdomen, and pelvis did not reveal any malignancy. MRI of her brain showed enhancement of the left cavernous sinus, optic nerve sheath, inferior rectus muscle, and posterior globe. Oral prednisone at a dose of 60 mg daily was initiated. On hospital day 3, fat-saturated MRI showed increased T2 signal and enhancement involving the left medial and inferior rectus muscles, as well as enhancement in the fat surrounding the left optic nerve sheath and extending to the posterior aspect of the globe and the superior orbital fissure **[Figure 1]**.

The patient's cranial nerve palsies improved with therapy throughout her 9-day admission **[Figure 2]**. She was discharged home with a plan to taper off prednisone over 2 months. Intravenous acyclovir was discontinued the day prior to discharge and she was transitioned to oral acyclovir for the remainder of her hospital stay. Antivirals were discontinued completely at discharge.

At 3 weeks postdischarge, the patient was doing well with no residual diplopia but with residual left mydriasis and ptosis.

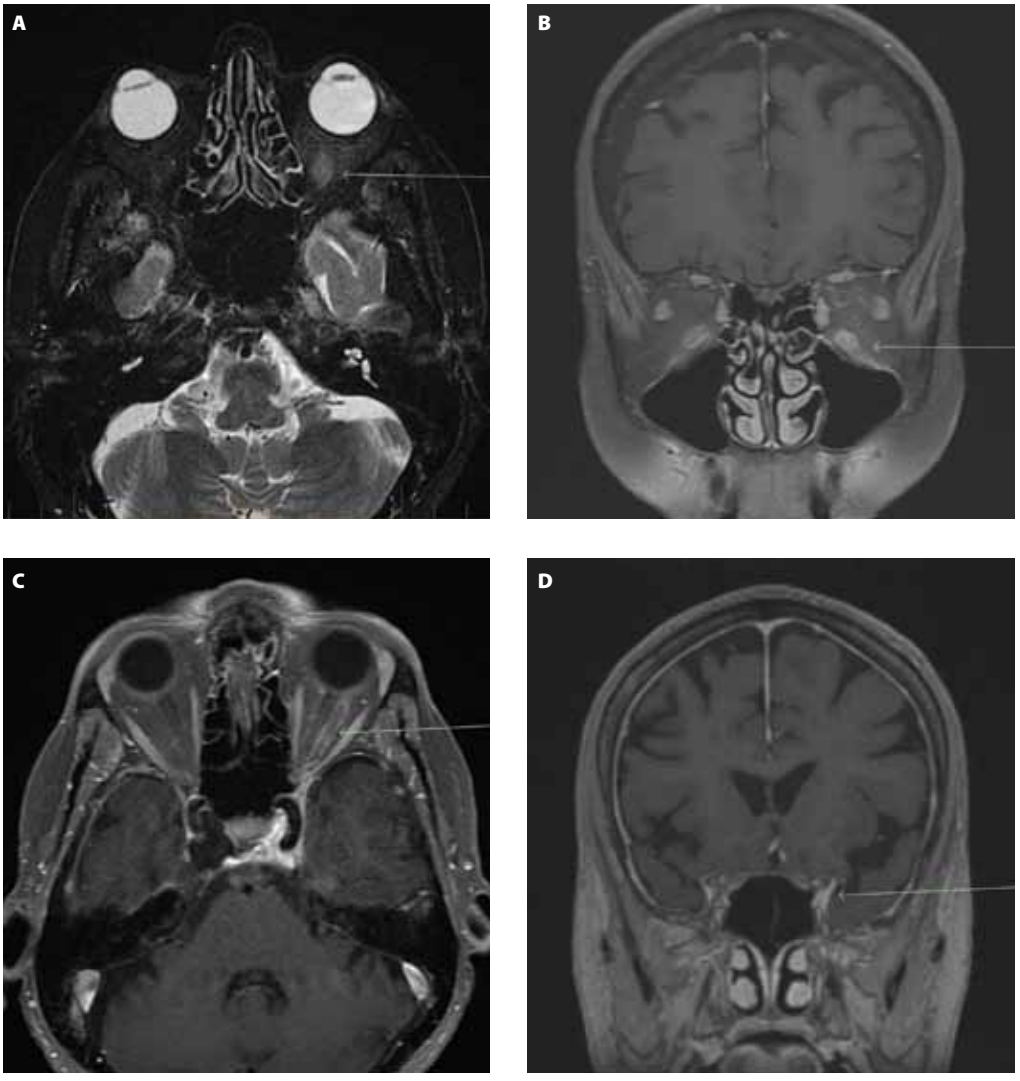

Figure 1. MRI of the orbit, showing left inferior rectus edema (A) and enhancement (B), retrobulbar enhancement (C), and superior orbital fissure enhancement (D).

Discussion

Varicella-zoster virus is the cause of chickenpox during primary infection and shingles during reactivation. Shingles usually affects one or more adjacent spinal or cranial sensory nerves, and typically leads to scattered rose-colored macules and vesicular lesions on the skin or mucous membrane supplied by the affected nerve.[1,2] Occasionally, VZV can reactivate in multiple contiguous sensory nerves, which is termed *multidermatomal zoster*. When noncontiguous dermatomes are involved, this is known as *herpes zoster duplex* (if two noncontiguous dermatomes are involved) or *herpes zoster multiplex* (if more than two noncontiguous dermatomes are involved).[3] Zoster is said to have cutaneous dissemination when more than 20 vesicles are found outside the primary and immediately adjacent dermatomes.[2] The risk of reactivation and dissemination is mediated primarily by a decline in VZV-specific memory T-cell activity, which occurs physiologically with aging or pathologically with immune suppression.[2,4,]

Although uncommon, the involvement of cranial motor nerves is well described—most famously the Ramsay Hunt syndrome, which occurs when VZV affects the geniculate ganglion and causes facial nerve palsy.[5] VZV can also affect the trigeminal nerve, and V1 involvement

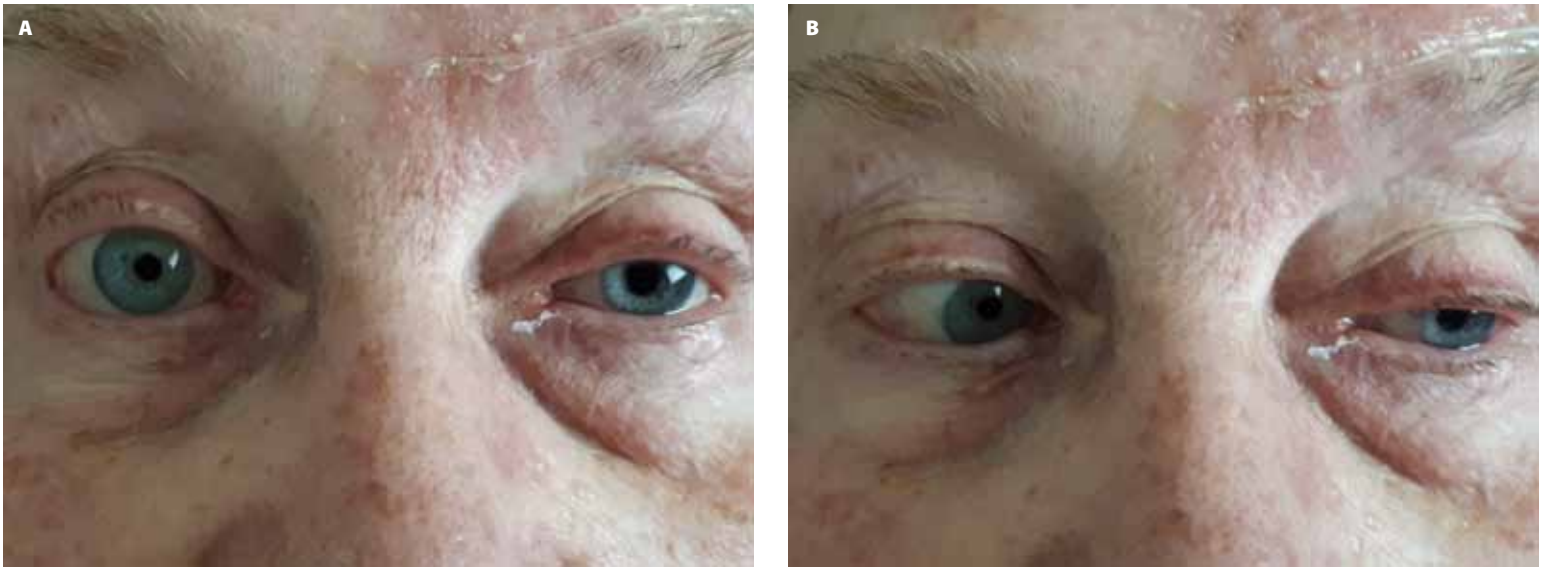

Figure 2. Central (A) and leftward (B) gaze on hospital day 3. Note left ptosis, mydriasis, and lateral rectus palsy, which had improved somewhat from the day of admission.

is known as *herpes zoster ophthalmicus*.[6] It is rare for VZV to affect multiple cranial nerves,[5,7] but when it does occur, it is usually associated with Ramsay Hunt syndrome.[5,8,9] There are only a few reports of VZV affecting multiple cranial nerves in the absence of facial nerve involvement.[6,10-13] In a retrospective analysis of 330 patients with herpes zoster with cranial nerve involvement, the frequency of trigeminal nerve involvement was 57.9%, while the frequency of oculomotor, trochlear, and abducens nerve involvement was 0.3% each.[7] We found no other cause of the patient's presentation other than VZV infection that affected multiple cranial nerves. Although the cerebrospinal fluid VZV polymerase chain reaction test was negative, it was performed after two adequate courses of oral antivirals, which may have reduced the sensitivity of viral PCR. Furthermore, CSF findings were consistent with aseptic meningitis, which is reported in 88% of patients with VZV ophthalmoplegia.[6]

VZV associated with partial or complete ophthalmoplegia generally involves variations of three clinical syndromes: orbital apex syndrome (OAS),[6,11,12] cavernous sinus syndrome (CSS),[14] and superior orbital fissure syndrome (SOFS).[10] OAS involves the oculomotor, trochlear, abducens, and optic nerves as well as the ophthalmic branch of the trigeminal nerve, and generally causes complete ophthalmoplegia and vision loss. CSS includes features of OAS with involvement of the maxillary branch of the trigeminal nerve and oculosympathetic fibres. SOFS is caused by lesions just anterior to the orbital apex and causes multiple cranial nerve palsies in the absence of optic nerve pathology.[15] The abnormal enhancement of the left cavernous sinus and optic nerve on the patient's MRI raised the possibility of CSS or OAS. However, the absence of complete ophthalmoplegia and optic nerve involvement was not in keeping with those diagnoses. It may be that early therapy with antivirals attenuated the disease severity and prevented complete ophthalmoplegia from developing.

Although immunocompromised patients are at higher risk of disseminated and visceral VZV,[2,16] a review of VZV-associated complete ophthalmoplegia found that immunocompetent and immunocompromised individuals were equally affected.[6] There is a lack of evidence to support or refute physicians searching for evidence of immunocompromise in patients with cranial nerve involvement of VZV, and the decision to pursue further testing of immune function is currently left to personal practice and individual patient risk.

Whether imaging findings can be used to dictate corticosteroid therapy is unclear.

The role of active VZV replication in CNS disease remains unclear. Some histopathologic studies of varicella encephalitis have suggested a postinfectious demyelinating process, whereas others have been consistent with direct viral pathology.[16] Similarly, both direct viral effect and postinfectious immunologic or inflammatory changes have been proposed as mechanisms for ophthalmoplegia in VZV infection.[6] In one report of orbital myositis associated with VZV, improvement was observed when the dose of prednisone was reduced and the dose of acyclovir was increased, which may be a sign that the presentation was caused by direct viral effect.[17] However, there are several reports of patient improvement after treatment with corticosteroids in conjunction with antivirals for VZV-associated ophthalmoplegia,[6,13,18] and there is a long history of corticosteroid use in cutaneous herpes zoster, with several reports of accelerated healing and reduced pain.[2]

Whether imaging findings can be used to dictate corticosteroid therapy is unclear. Perineuritis, demyelination, contiguous orbital inflammation, cranial vasculitis, myositis, encephalitis, and meningitis have been reported to be in keeping with an underlying immune

mechanism,[6] and these findings on neuroimaging might sway a physician toward treatment with prednisone. Optic perineuritis and orbital inflammation were present on neuroimaging of our patient. This report highlights the use of corticosteroids to good effect in an immunocompetent woman with VZV-associated partial ophthalmoplegia and lends more support to the use of corticosteroids (in conjunction with antivirals) in select patients. Clinicians should be aware of this rare complication of VZV infection and should consider the use of corticosteroids once other infectious causes have been ruled out.

Summary

Varicella zoster can affect both sensory and motor cranial nerves, and is a rare cause of complete or partial ophthalmoplegia in both immunocompromised and immunocompetent patients. The underlying mechanism of cranial nerve involvement is unknown but may involve direct viral infection and postinfectious inflammation of the cranial nerves. There is little evidence to guide treatment of varicella-zoster virus ophthalmoplegia, but the use of corticosteroids in addition to antivirals may target inflammation involved in the pathogenesis of this condition. ■

Acknowledgments

The authors kindly thank Dr Melina Warren for her expert interpretation of the imaging studies and her help in selecting images for this report.

Competing interests

None declared.

There is little evidence to guide treatment of varicella-zoster virus ophthalmoplegia, but the use of corticosteroids in addition to antivirals may target inflammation involved in the pathogenesis of this condition.

References

1. Schmader KE, Oxman MN. Chapter 194. Varicella and herpes zoster. In: Goldsmith LA, Katz SI, Gilchrest BA, et al., editors. Fitzpatrick's dermatology in general medicine. 8th ed. New York, NY: McGraw-Hill; 2012.
2. McCrary ML, Severson J, Tyring SK. Varicella zoster virus. J Am Acad Dermatol 1999;41:1-14.
3. Rodríquez-Lomba E, Sánchez-Herrero A, Suárez-Fernández R, Pulido-Pérez A. La excepcion que confirma la regla: herpes zoster duplex y multiplex. Actas Dermosifiliogr 2019;110:690-693.
4. Weinberg A, Levin MJ. VZV T cell-mediated immunity. In: Abendroth A, Arvin A, Moffat J, editors. Varicella-zoster virus. Current topics in microbiology and immunology. Vol 342. Berlin, Heidelberg: Springer; 2010. p. 341-357.
5. DE Sylva Plk, Rajpathak SD, Borgohain BN, et al. Multiple cranial nerve involvement in herpes zoster (A case report). Med J Armed Forces India 1998;54:51-52.
6. Sanjay S, Chan EW, Gopal L, et al. Complete unilateral ophthalmoplegia in herpes zoster ophthalmicus. J Neuroophthalmol 2009;29:325-337.
7. Tsau P-W, Liao M-F, Hsu J-L, et al. Clinical presentations and outcome studies of cranial nerve involvement in herpes zoster infection: A retrospective single-center analysis. J Clin Med 2020;9:946.
8. Lin Y-Y, Kao C-H, Wang C-H. Varicella zoster virus infection of the pharynx and larynx with multiple cranial neuropathies. Laryngoscope 2011;121:1627-1630.
9. Niesvizky-Kogan I, Greca I, Gambhir HS. Varicella zoster presenting as cranial polyneuropathy. Am J Emerg Med 2019;37:564.e5-564.e6.
10. Gupta D, Vishwakarma SK. Superior orbital fissure syndrome in trigemino-facial zoster. J Laryngol Otol 1987;101:975-977.
11. Kurimoto T, Tonari M, Ishizaki N, et al. Orbital apex syndrome associated with herpes zoster ophthalmicus. Clin Ophthalmol 2011;5:1603-1608.
12. Lee C-Y, Tsai H-C, Lee SS-J, Chen Y-S. Orbital apex syndrome: An unusual complication of herpes zoster ophthalmicus. BMC Infect Dis 2015;15:33.
13. Im M, Kim BJ, Seo YJ, et al. Complete ophthalmoplegia after herpes zoster. Clin Exp Dermatol 2007;32:162-164.
14. Amato-Watkins A, St. George EJ, Saxena A, Bhattacharya J. Carotico-cavernous fistula secondary to varicella zoster? Br J Neurosurg 2010;24:298-300.
15. Yeh S, Foroozan R. Orbital apex syndrome. Curr Opin Ophthalmol 2004;15:490-498.
16. Gnann Jr. JW. Varicella-zoster virus: Atypical presentations and unusual complications. J Infect Dis 2002; 186:S91-S98.
17. Badilla J, Dolman PJ. Orbital myositis involving the oblique muscles associated with herpes zoster ophthalmicus. Ophthalmic Plast Reconstr Surg 2007;23:411-413.
18. Lexa FJ, Galetta SL, Yousem DM, et al. Herpes zoster ophthalmicus with orbital pseudotumor syndrome complicated by optic nerve infarction and cerebral granulomatous angiitis: MR-pathologic correlation. Am J Neuroradiol 1993;14:185-190.