Clinical features of Varicella Zoster Virus infection of the nervous system

Varicella zoster virus (VZV) is an exclusively human neurotropic herpesvirus that causes approximately four million cases of chickenpox annually. After chickenpox, VZV becomes latent in cranial nerve, dorsal root and autonomic nervous system ganglia along the entire neuraxis. The neurological complications of VZV reactivation are shown in Fig. 1.

Zoster. Virus reactivation, mostly in elderly and immunocompromised individuals, produces zoster (shingles), characterised by severe sharp, lancinating, radicular pain and rash restricted to 1-3 dermatomes. In affected dermatomes, sensation is decreased, yet the skin is exquisitely sensitive to touch (allodynia). In the US, more than 500,000 cases occur annually. Although varicella occurs mostly in Spring, zoster develops any time of year. The incidence of recurrent zoster in immunocompetent individuals is less than 5%. Thoracic zoster is most common, followed by facial lesions, usually in the ophthalmic division of the trigeminal nerve and frequently accompanied by zoster keratitis, a potential cause of blindness if not recognised and treated promptly. Patients with ophthalmal zoster need immediate slit-lamp examination by an ophthalmologist, particularly if skin lesions extend to the medial side of the nose (Hutchinson's sign). Zoster in the maxillary and mandibular divisions of the trigeminal nerve may be associated with osteonecrosis and spontaneous tooth exfoliation. Facial nerve involvement, characterised by weakness of all facial muscles on one side, usually develops with rash in the ipsilateral external ear (zoster oticus) or hard palate. Zoster oticus with peripheral facial weakness constitutes the Ramsay Hunt syndrome (Sweeney and Gilden, 2001) from which recovery of facial paralysis is often less complete than in idiopathic Bell's palsy. Zoster may also be accompanied by ophthalmoplegia, most commonly affecting the third cranial nerve, or by optic neuritis, or both. Lower cranial nerve palsies are less frequent. Cranial neuropathy often occurs weeks after acute zoster. Since all cranial nerves receive their blood supply from the carotid circulation via small branches supplying groups of two or three cranial nerves (Lapsesle and Lasjaunias, 1986), the occurrence of concurrent contiguous cranial neuropathies suggests small vessel-mediated infarction. VZV may spread transaxially along trigeminal and other ganglionic afferent fibers from the carotid arteries (Mayberg et al., 1984) to the vasa vasorum of small nerves. Cervical zoster is occasionally associated with arm weakness (zoster paresis) and less often with diaphragmatic paralysis. Lumbosacral zoster can be accompanied by leg weakness as well as bladder and bowel dysfunction. Zoster has developed within days-weeks after injury by lightning or injection of foreign material, and one time five hours after spinal anaesthesia (Arnold, 1941).

Treatment. No protocol is universally accepted. Analgesia includes extra-strength acetaminophen and codeine 30-60 mg every 6 hours when necessary. Oral acyclovir (800 mg 5 times daily) or famciclovir (500 mg 3 times daily) decreases new lesion formation and reduces acute pain (Tyring et al., 1993; Wood et al., 1994).

We prescribe oral acyclovir or famciclovir for 7 days if new skin lesions have developed within the past week. Patients with ophthalmic distribution zoster should receive antivirals for at least 7 days.

Postherpetic Neuralgia (PHN). Pain that persists for months and sometimes years (PHN) develops in >40% zoster patients over age 60. Because the elderly and immunocompromised patient population is increasing, VZV can be seen as an important infection of the twenty-first century.

Prevention. We give acyclovir (800 mg 5 times daily) or famciclovir (500 mg 3 times daily) to zoster patients over age 60 for 7-10 days. No optimum therapy to prevent PHN exists. Various trials used antivirals, steroids, or both, as well as amantadine hydrochloride (a dopamine agonist); parenteral adenosine monophosphate; and a double-blind study with either oral levodopa and benserazide or placebo demonstrated some efficacy in preventing PHN. However, studies were hampered by potential toxic side effects (as with interferon), a small sample size, and an abnormally high incidence of PHN in control groups (reviewed in Gilden et al., 2000).

Treatment of PHN. Like zoster, no universally accepted treatment exists. Tricyclic antidepressants, such as amitriptyline or nortriptyline (25-75 mg at night), and anticonvulsants carbamazepine (600-1200 mg daily), phenytoin (300-600 mg daily) and gabapentin (neurontin), 900-3600 mg daily relieve pain in some patients along with slow release oxycodeone 10-50 mg twice daily. A short course of steroids, e.g. prednisone (40-60 mg daily for 3-5 days and sometimes longer), may reduce inflammation contributing to pain. Topical lidocaine patches as well as aspercreme and flexall 454 may help. The development of other topical anaesthetic agents for PHN sufferers is an important area for future clinical research.

VZV Vasculopathy. In immunocompetent and immunocompromised patients, central nervous system (CNS) complications develop after VZV reactivation when virus spreads to arteries of the brain and spinal cord. Although VZV infection in the CNS is commonly referred to as VZV encephalitis, it is actually a vasculopathy that affects large and small cerebral arteries. Large artery infection predominates in elderly immunocompetent individuals, and is characterised by acute focal deficit that develops weeks-months after contralateral trigeminal-distribution zoster. The vasculopathy is usually restricted to 1-3 large anterior circulation arteries. In contrast, VZV infection of small cerebral blood vessels predominates in immunocompromised individuals and produces features of headache, fever, mental status changes and multifocal deficit, evident by neurological exam and brain MRI imaging. VZV small-vessel disease is often chronic and may develop without zoster rash. Both ischaemic and hemorrhagic infarcts are found in cortical, subcortical gray and white matter (Amie-LeFond et al., 1995).

Most patients with VZV vasculopathy have a cerebral spinal fluid (CSF) pleocytosis, usually <100 cells (predominantly mononuclear), oligoclonal bands and increased CSF IgG. When large vessels are involved, angiography reveals focal constriction and segmental narrowing. Microscopic and virologic examination of arteries reveals inflammation, multinucleated giant cells, Cowdry A inclusions and herpesvirus particles (all hallmarks of herpesvirus infection), as well as VZV DNA in affected vessels (Gilden et al., 1996; Melanson et al., 1996).

Because VZV vasculopathy is uncommon, controlled treatment trials...
have not been possible. Based on the presence of virus in arteries and variably associated inflammation, we recommend intravenous acyclovir (10-15 mg/kg 3 times daily for 7-10 days) to kill persistent virus, and a short course of steroids (prednisone 60-80 mg daily for 3-5 days) for their anti-inflammatory effect. Immunocompromised patients may need prolonged oral antiviral therapy.

**VZV Myelitis.** VZV myelitis develops in immunocompetent and immunocompromised patients. In immunocompetent individuals, myelitis is usually monophasic and occurs 1-2 weeks after acute varicella or zoster. Clinical features are characterised by paraparesis with a sensory level and sphincter impairment. The mechanism of post-infectious myelitis is unknown. In contrast, VZV myelitis in immunocompromised patients is often insidious, progressive and sometimes fatal. Spinal cord MRI shows longitudinal serpiginous enhancing lesions. Spinal cord necrosis and intense inflammation with parenchymal invasion by VZV are seen pathologically. Cases of chronic and recurrent VZV myelopathy, responsive to antiviral treatment, have been reported (Gilden et al., 1994a). Like VZV vasculopathy in brain, patients with VZV myelitis do not always have rash. Thus, an early search for VZV DNA or antibody in CSF is essential for diagnosis, particularly since acyclovir treatment, even in AIDS patients, may clear infection.

**VZV Infection without Rash.** Zoster sine herpete is dermatomal-distribution pain without antecedent rash. Before polymerase chain reaction (PCR), verification was by serologic testing. The first documentation was a physician who described his acute trigeminal distribution pain without rash. The first documentation was a physician who described his acute trigeminal distribution pain without rash, associated with a four-fold rise in antibody to VZV, but not to herpes simplex virus (HSV) (Easton, 1970). Demonstration of virus came only after PCR analysis of 2 men without rash who had experienced prolonged thoracic-distribution radicular pain. Amplifiable VZV DNA, but not HSV DNA, was found in their CSF and blood mononuclear cells (MNCs) (Gilden et al., 1994b). Both were treated successfully with intravenous acyclovir. The prevalence of zoster sine herpete awaits virological analysis of additional patients with prolonged radicular pain. Analysis should include PCR to amplify VZV DNA in CSF and blood MNCs as well as a search for VZV antibody in CSF. The existence of ganglionitis without rash is further supported by radicular pain before zoster, so-called preherpetic neuralgia. A report of 6 individuals with preherpetic neuralgia exists. Pain preceded rash by 7-100 days, and was located in dermatomes different from, as well as the area of eventual rash (Gilden et al., 1991).

There are other instances of VZV infection without rash. VZV meningitis and meningoencephalitis without rash were verified by detection of VZV antibody synthesised intrathecally (Vardal et al., 1982). Two instances of polyneuritis cranialis produced by VZV in apparently immunocompetent men were documented by seroconversion to VZV, but not to multiple other human viruses (Mayo and Booss, 1989; Osaki et al., 1995). Some cases of acute unilateral facial (Bell's) palsy that developed without rash were attributed to VZV (geniculate zoster sine herpete) based on seroconversion (Aitken and Brain, 1933). The most extreme example of VZV infection of the nervous system without rash was an immunocompromised man who developed meningoradiculitis and died 3 weeks later (Dueland et al., 1991). At autopsy, hemorrhagic inflammatory lesions with Cowdry A inclusions were found in meninges and nerve roots extending from cranial nerve roots to cauda equina. VZV, but not HSV or...
References

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Varicella-Zoster Virus

Virology and Clinical Management

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Published in association with the VZV Research Foundation, this is a comprehensive account of the biology and clinical features of the varicella-zoster virus - it surveys current knowledge of the molecular biology, pathogenesis and clinical features of VZV as the causative agent of chickenpox and zoster (shingles).

Topics covered include viral replication, latency, immune mechanisms, epidemiology and disease manifestations, and complications of varicella and zoster. There is detailed information on live attenuated varicella vaccine, treatment strategies and the management of postherpetic pain in zoster patients.

This book will appeal to a wide range of clinicians and investigators, including neurologists, paediatricians, dermatologists and infectious disease specialists, as well as virologists interested in the herpes viruses.

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Review Article
cytomegalovirus antigen and nucleic acid, was detected in all infected tissue.

VZV Diagnosis: Amplifiable VZV DNA by PCR and Antibody to VZV. PCR and antibody testing of CSF to confirm the role of VZV in producing the many varied clinical syndromes of the peripheral and central nervous system is widely available and should be exploited, particularly since effective antiviral therapy exists. In the appropriate clinical setting (i.e. acute or subacute spinal cord disease, acute or chronic progressive encephalitis, or chronic radicular pain with or without rash), the presence of VZV DNA or antibody, or both, in CSF is strong presumptive evidence of infection. Even the detection of VZV antibody in CSF without PCR-amplifiable VZV DNA supports the diagnosis of VZV infection of the nervous system (Gilden et al., 1998).

Analysis of serum anti-VZV antibody alone is of no value since VZV antibodies are present in nearly all adults (Vafai et al., 1988).

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