Review Article

Medical Progress

Neurologic Complications of the Reactivation of Varicella–Zoster Virus

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VARICELLA–ZOSTER virus is an exclusively human herpesvirus that causes chickenpox (varicella), becomes latent in cranial-nerve and dorsal-root ganglia, and frequently reactivates decades later to produce shingles (zoster) and postherpetic neuralgia. In immunocompetent elderly persons or immunocompromised patients, varicella–zoster virus may produce disease of the central nervous system.

Since the last major review of varicella–zoster virus in the *Journal*,[1,2] advances in molecular biology have provided important new insights into the pathogenesis of infection with varicella–zoster virus. The detection of varicella–zoster virus in blood vessels and other tissues by methods based on the polymerase chain reaction (PCR) has widened the recognized clinical spectrum of acute and chronic disorders associated with varicella–zoster virus, including latent infections. In this article we highlight current progress in understanding the latency of varicella–zoster virus and review the neurologic complications of viral reactivation, with a focus on previously underemphasized patterns of zoster, preherpetic and postherpetic neuralgia, myelitis, large-vessel granulomatous arteritis, and small-vessel encephalitis, all of which may occur without the rash typical of zoster (Fig. 1).

LATENCY

In latency, the condition that follows acute infection (usually manifested as chickenpox), the virus persists in a noninfectious form with intermittent periods of reactivation and shedding. Varicella–zoster virus reactivates with increasing age or immunosuppression of the infected person; however, the biologic mechanisms that underlie the transition from latency to active viral replication are unknown. Many laboratories have made serious efforts to determine the physical state of the virus during latency, because understanding this state is essential to predicting or preventing the neurologic complications produced by reactivation of the virus.

DNA of Varicella–Zoster Virus in Human Ganglia

After it has produced chickenpox, varicella–zoster virus becomes latent in ganglia along the entire neuraxis. Unlike herpes simplex virus, however, varicella–zoster virus cannot be cultured from human ganglia.[3] Although clinicians had long suspected that the ganglia were the site of latency, verification came only after latent varicella–zoster virus was detected in human trigeminal and thoracic ganglia by means of Southern blot analysis and in situ hybridization.[4-6] A PCR analysis that revealed varicella–zoster viral DNA in trigeminal ganglia from 13 of 15 subjects and in thoracic ganglia from 9 of 17 subjects[7] validated earlier observations that the thoracic and trigeminal dermatomes were the most common sites of reactivation.[8]

Most, if not all, of the DNA molecule of varicella–zoster virus is present during latency,[7] but the viral burden is low. A competitive PCR assay revealed 6 to 31 copies of varicella–zoster viral DNA in 10^5 ganglionic cells.[9] A noncompetitive PCR assay indicated more varicella–zoster viral DNA,[10] similar to the 10^3 to 10^5 copies of latent DNA of herpes simplex virus type 1 in 10^5 cells.[11] The difference in the number of varicella–zoster viral copies reported[9,10] may result from the fact that different techniques were used. Latent varicella–zoster viral DNA is extrachromosomal (nonintegrated), possibly in a circular or concatameric (end-to-end) configuration,[10] as is the DNA of latent herpes simplex virus type 1.[12] During latency, RNA corresponding to varicella–zoster viral genes *21, 29, 62,* and *63*[13] and proteins corresponding to varicella–zoster viral genes *4, 21, 29, 62,* and *63* have been detected in the cytoplasm of neurons.[14,15]

Cell Type That Harbors Latent Varicella–Zoster Virus

Most studies indicate that neurons are the primary, if not exclusive, site of latent virus. In situ hybridization alone or together with PCR detected varicella–zoster virus only in neurons initially,[5,6] later in perineuronal satellite cells,[16,17] and then in both neurons and non-neuronal cells of latently infected human ganglia.[18] Two further studies found varicella–zoster virus predominantly in neurons.[19,20] A different strategy, in which quantitative PCR analysis was used to study neurons and non-neuronal cells from postmortem

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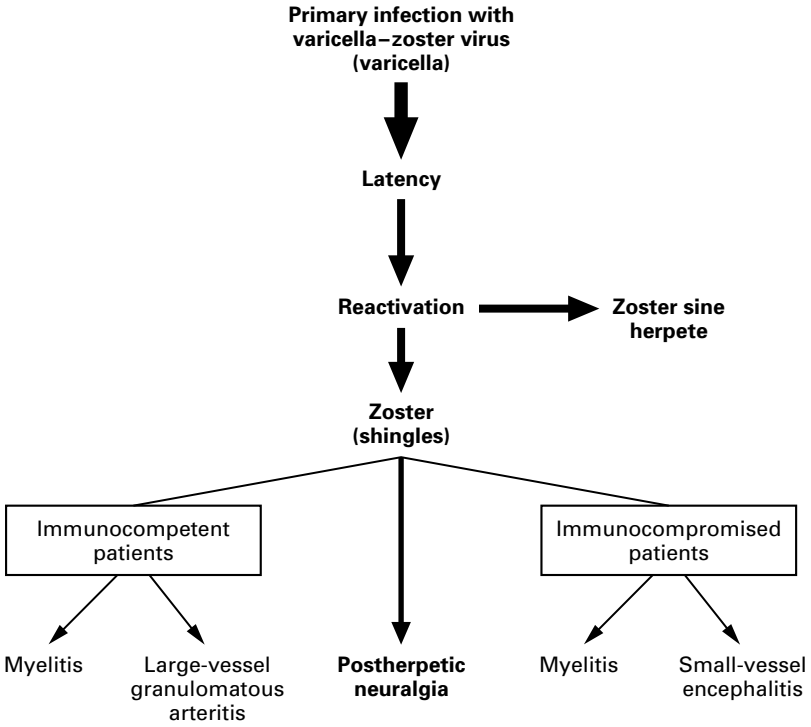

Figure 1. Neurologic Complications of the Reactivation of Varicella–Zoster Virus.

The primary encounter (infection) with varicella–zoster virus usually occurs in childhood and produces chickenpox (acute varicella). After producing chickenpox, varicella–zoster virus becomes latent in ganglia in virtually all people who have had chickenpox and remains present for the lifetime of the person. The reactivation of varicella–zoster virus, usually after the patient is 50 years of age, produces the characteristic dermatomal rash of shingles (zoster). Rarely, the reactivation of varicella–zoster virus can also produce pain without rash (zoster sine herpete). In immunocompetent patients, the main complication of zoster is postherpetic neuralgia (pain that persists more than six weeks after the development of rash). In rare instances, myelitis or large-vessel granulomatous arteritis, which produces disease of the central nervous system, may develop in immunocompetent patients. After immunocompromised patients have zoster, there may be more severe complications of the central nervous system in the form of progressive small-vessel encephalitis or myelitis. Each of these complications can develop without clinically recognized rash, although they do so infrequently.

ganglia that had been sorted according to size, revealed two to five copies of varicella–zoster viral DNA that were primarily, if not exclusively, in neurons.[21]

Even though a considerable amount of information has been acquired about the physical state of varicella–zoster virus in latently infected ganglia, none of this information has yet been found to be directly applicable to treating human disease. A better understanding of viral latency will produce testable hypotheses designed to prevent the reactivation of varicella–zoster virus and its neurologic complications. Millions of children worldwide have received a live attenuated vaccine against varicella–zoster virus. The virus in the vaccine becomes latent and can reactivate, however.[22] Thus, the widespread use of a vaccine against varicella–zoster virus is not likely to result in a reduced incidence of zoster and its attendant complications. Therefore, trials of a vaccine to boost immunity in middle age are already under way.[23]

COMPLICATIONS IN THE PERIPHERAL NERVOUS SYSTEM

Zoster (Shingles, Radiculoneuropathy, and Ganglionitis)

More than 300,000 cases of zoster occur annually in the United States, mostly in elderly and immunocompromised patients. Varicella occurs mostly in the spring, but zoster develops throughout the year. A patient in whom varicella develops before 1 year of age is predisposed to zoster before 60 years of age.[24] Zoster develops 8 to 10 times as frequently at or after 60 years of age as before. Thirteen percent of Americans are older than 65; this proportion is increasing, so the rate of zoster-associated complications will also increase. The incidence of recurrent zoster in immunocompetent patients is less than 5 percent.[8]

Zoster is characterized by severe sharp, lancinating, radicular pain and rash. The pain is associated with itching and dysesthesias. In affected dermatomes, sen-

sation is decreased, yet the skin is exquisitely sensitive to touch (allodynia). Any level of the neuraxis can be affected. The thorax is the most common site, followed by the face. Facial lesions are usually present in the ophthalmic division of the trigeminal nerve and are frequently accompanied by keratitis, which is a potential cause of blindness if not recognized and treated promptly. Patients with ophthalmic zoster need to undergo immediate slit-lamp examination by an ophthalmologist, particularly if skin lesions extend to the nose (Hutchinson's sign).

Zoster in the maxillary and mandibular divisions of the trigeminal nerve may be associated with osteonecrosis and spontaneous exfoliation of teeth in adults[25] and children.[26] When the seventh cranial nerve is involved, there is weakness of all facial muscles on one side, along with rash in the ipsilateral external ear (zoster oticus) or hard palate. Vesicles in these sites are often not looked for. Zoster oticus and peripheral facial weakness together constitute the Ramsay Hunt syndrome. In our experience, recovery from facial weakness or paralysis is less complete than in idiopathic Bell's palsy.

Zoster may also be accompanied by ophthalmoplegia (most commonly affecting the third cranial nerve), optic neuritis, or both.[27] Palsies of the lower cranial nerve occur less frequently.[28,29] Cranial neuropathy often occurs weeks after acute zoster has developed. Because all cranial nerves are supplied by blood from the circulation of the carotid artery through small branches that supply groups of two or three cranial nerves,[30] the occurrence of concurrent, contiguous cranial neuropathies suggests infarction mediated by small vessels. Varicella–zoster virus may spread transaxonally along trigeminal and other ganglionic afferent fibers from the carotid arteries[31] to the vasa vasorum of small nerves.

Cervical zoster is occasionally associated with arm weakness[32] (zoster paresis) and less often with diaphragmatic paralysis.[33] Lumbosacral zoster can be accompanied by leg weakness as well as bladder and bowel dysfunction. In rare instances, zoster has developed within days to weeks after injury by lightning or injection of foreign material, and a case of zoster that occurred five hours after spinal anesthesia has been reported.[34] The histologic hallmark of zoster is inflammation and neuronal loss in ganglia that correspond to the segmental distribution of rash. Intense lymphocytic inflammation and vasculitis in nerves cause degeneration of motor and sensory roots and may spread into adjacent parts of the spinal cord, with localized leptomeningitis and gray-matter necrosis of varying degrees or demyelination.[35]

Treatment of Zoster

Comprehensive reviews of treatment for acute zoster and postherpetic neuralgia have been published,[36-39] although no protocol is universally accepted. Analgesic treatment usually includes extra-strength acetaminophen and 30 to 60 mg of codeine every six hours when necessary; stronger narcotics should be avoided. The administration of famciclovir (500 mg three times daily) or oral acyclovir (800 mg five times daily) decreases the formation of new lesions and reduces acute pain.[40,41] The efficacy of antiviral therapy, especially in immunocompetent patients who are younger than 50 years of age, remains to be established. In our practice, we prescribe famciclovir or oral acyclovir for seven days if new skin lesions have developed within the previous week. Patients with zoster in an ophthalmic distribution should receive antiviral drugs for at least seven days. The current cost of a one-week treatment with generic drugs is $28 to $75 for acyclovir and $138 to $150 for famciclovir in the doses listed above.

Postherpetic Neuralgia

Prevention

Most complications of zoster manifest as postherpetic neuralgia, which is pain that persists more than six weeks after the development of rash. Postherpetic neuralgia develops slightly more frequently in women than in men,[42] and it occurs after zoster in a trigeminal distribution.[42-44] Once postherpetic neuralgia disappears, it does not recur. Age is the most important factor in predicting its occurrence. Postherpetic neuralgia does not occur before 50 years of age; therefore, immunocompetent young adults and children with zoster probably do not need antiviral therapy aimed at preventing this sequela. Postherpetic neuralgia can develop in patients who are 50 or older[45]; after the age of 60, more than 40 percent of patients with zoster will have the condition.[43-45] Controlled trials of oral antiviral drugs to prevent postherpetic neuralgia have not been shown to be effective after six months of treatment.[39] Nevertheless, acyclovir (800 mg five times daily) or famciclovir (500 mg three times daily) is given empirically to patients with zoster who are older than 60 years of age for 7 to 10 days in addition to medication for pain.

Despite numerous trials, the optimal therapy for preventing postherpetic neuralgia has not been determined. Most studies have focused on antiviral drugs, steroids, or both. Drugs on which studies have been undertaken include interferon alfa-n3 (in intramuscular injections),[46] acyclovir (800 mg taken orally five times daily for 7 days),[47] acyclovir (taken for 7 or 21 days, with or without prednisone, in a randomized, double-blind trial),[41] amantadine hydrochloride (a dopamine agonist, in a well-controlled trial),[48] adenosine monophosphate (administered parenterally in a controlled study),[49] and either oral levodopa and benserazide or placebo (in a double-blind study).[50] Although these trials demonstrated some efficacy in preventing postherpetic neuralgia, they were hampered by potentially toxic side effects (as with interferon), small

samples, and an abnormally high incidence of postherpetic neuralgia in the control groups.

Steroids used to prevent postherpetic neuralgia have included oral triamcinolone,[51] prednisolone (40 mg daily),[52] and prednisolone with or without acyclovir.[53] No difference between treatment groups was observed. Again, small study populations and an abnormally high incidence of postherpetic neuralgia in the control groups were flaws in these trials. Further studies with larger numbers of patients are needed to assess the efficacy, if any, of steroids in preventing postherpetic neuralgia.

Treatment

Like zoster, postherpetic neuralgia has no universally accepted treatment. Chronic pain produces intense suffering and changes in lifestyle in elderly, often fragile, patients. Much effort has been expended in the attempt to identify effective therapy. More than 40 pharmacologic, antiseptic, and surgical therapies have been tried, with limited success; these include aspirin, hormones, narcotics, vitamins, immunoglobulins, radiotherapy, and nerve blocks or excision.[37] A review has summarized controlled trials of neuroactive drugs used to treat postherpetic neuralgia.[39] Tricyclic antidepressants, such as amitriptyline or nortriptyline (25 to 75 mg per day), and the anticonvulsants carbamazepine (400 to 1200 mg daily) and phenytoin (300 to 400 mg daily) relieve pain in some patients. An anecdotal report described dramatic improvement in one patient treated with gabapentin (300 mg three times a day).[54]

Some clinicians advocate a short course of steroids (for example, prednisone at a dose of 40 to 60 mg daily for three to five days and sometimes longer) to reduce inflammation that may be contributing to pain. The subcutaneous infusion of ketamine reduced postherpetic neuralgia but was associated with intolerable side effects.[55] Topical aspirin in chloroform helped relieve pain from zoster and postherpetic neuralgia.[56] The development of anesthetic agents designed for topical use in postherpetic neuralgia is an important area for future clinical research.

Mechanisms

In affected dermatomes, the threshold for provoking any sensation is raised; once sensation is produced, however, it is painful. Although the precise mechanism is unknown, neuronal perturbation by virus may be involved in the pathogenesis of pain. Microscopical studies of ganglia from two patients with postherpetic neuralgia revealed inflammatory infiltrates, often around dying neurons, one to two years after the development of acute zoster.[57,58] Further pathological and virologic analysis of ganglia obtained at autopsy from patients with postherpetic neuralgia is needed. The level of productive viral infection in ganglia during postherpetic neuralgia is unknown. Normally, after the resolution of acute zoster, varicella–zoster virus returns to the latent state. In immunocompetent patients with zoster who do not have postherpetic neuralgia, varicella–zoster viral DNA can be detected in blood up to six weeks after the development of rash, coinciding with the period of pain.[59] The detection of virus in mononuclear cells in blood may reflect the viral burden in ganglia. In patients with postherpetic neuralgia, varicella–zoster virus may persist in ganglia at a greater level than during latency.

Supporting this concept is the detection of varicella–zoster viral DNA in mononuclear cells of some patients with postherpetic neuralgia but not in mononuclear cells of patients with zoster who do not have postherpetic neuralgia or in elderly patients with no history of zoster.[60] Mononuclear cells moving through the ganglia of patients with postherpetic neuralgia may encounter and engulf viruses whose DNA can be amplified (Fig. 2). If the viral burden were shown to be greater in ganglia from patients who had postherpetic neuralgia before they died than in latently infected ganglia from patients with zoster who did

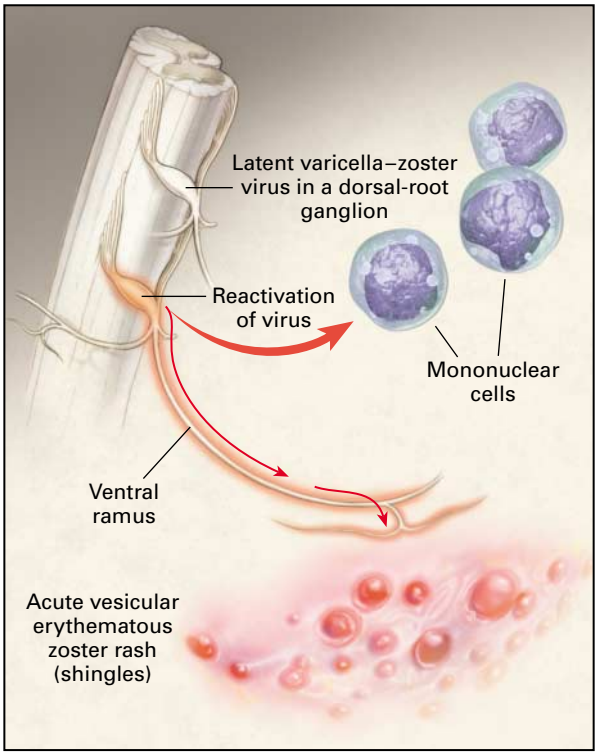

Figure 2. Latent and Reactivated Varicella–Zoster Virus.
Shown are latent virus in a dorsal-root ganglion (white fusiform swelling) adjacent to the spinal cord and reactivated virus in a nearby dorsal-root ganglion (orange fusiform swelling) with transaxonal spread to the skin, causing acute vesicular erythematous zoster rash.

not have postherpetic neuralgia,[9] there would be a rationale for the aggressive treatment of postherpetic neuralgia with antiviral agents.

COMPLICATIONS IN THE CENTRAL NERVOUS SYSTEM

After varicella or zoster develops, varicella–zoster virus usually remains within ganglia. Sometimes, after reactivation in either immunocompetent or, especially, immunocompromised patients, the virus spreads to the spinal cord and brain. Severely immunocompromised patients have the most severe complications of reactivation, the greatest depth of tissue penetration, and the greatest amounts of recoverable virus.

Myelitis

In immunocompetent patients, myelitis may complicate acute varicella or zoster, usually one to two weeks after the development of rash. Its clinical features are paraparesis with a sensory-level and sphincter impairment. The cerebrospinal fluid either is normal or shows mild pleocytosis with a normal protein level or a mild elevation. T_2-weighted magnetic resonance imaging reveals hyperintense lesions, sometimes with focal swelling of the spinal cord. The condition of most patients improves substantially, but some patients have persistent stiffness and weakness of the legs. Because most immunocompetent patients survive, the pathology of this form of transverse myelitis is unknown. Further virologic and immunologic verification is needed; varicella–zoster virus cannot be cultured from cerebrospinal fluid, although PCR has revealed varicella–zoster viral DNA in cerebrospinal fluid.

In immunocompromised patients, myelopathy is often more insidious and progressive, and it is sometimes fatal. Magnetic resonance imaging of the spinal cord shows focal (Fig. 3) or longitudinal serpiginous enhancing lesions.[61] On autopsy, spinal cord necrosis and intense inflammation with parenchymal invasion by varicella–zoster virus have been found. Long-term use of low-dose steroids may cause a predisposition to myelitis and encephalitis caused by varicella–zoster virus.[62-64]

Myelitis due to varicella–zoster virus was formerly diagnosed through its close temporal relation to rash. The recent detection of varicella–zoster viral DNA or antibody to varicella–zoster virus in cerebrospinal fluid indicated that acute, and even recurrent, myelopathy can develop without rash.[61] We reported a case in which myelopathy developed in a patient five months after zoster, at which time amplifiable varicella–zoster viral DNA was detected in cerebrospinal fluid. Myelopathy developed in another patient while acute zoster was present; the myelopathy resolved but recurred six months later. Five months after recurrence, the patient's cerebrospinal fluid contained both varicella–zoster viral DNA and antibody to varicella–zoster virus.[61] Overall, the severity of myelopathy from varicella–zoster virus ranges from acute to chronic, and the condition rarely recurs. An early search for varicella–zoster viral DNA or antibody in cerebrospinal fluid is essential for diagnosis, particularly because aggressive treatment with acyclovir, even in patients with the acquired immunodeficiency syndrome (AIDS), may produce a favorable response.[65]

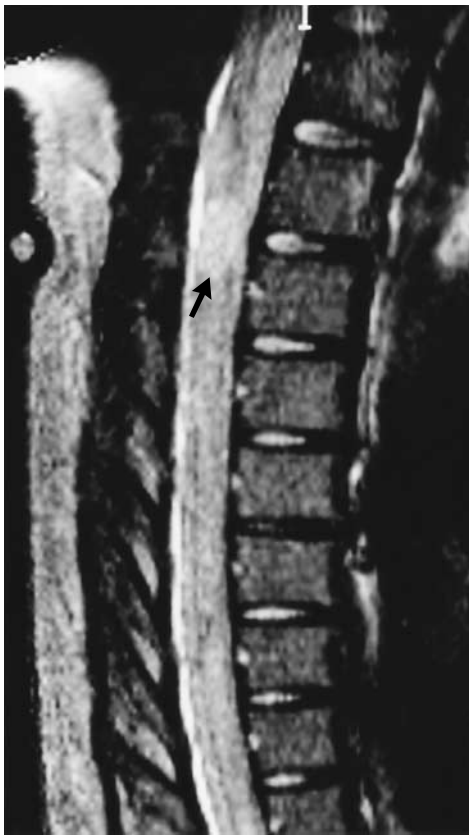

Figure 3. Magnetic Resonance Image of the Spinal Cord Showing Myelitis Caused by Varicella–Zoster Virus in an Immunocompetent Patient.

Paraplegia occurred shortly after the development of zoster rash. A gadolinium-enhanced lesion (arrow) can be seen in the thoracic spinal cord.

Encephalitis and Arteritis

Older literature described an uncommon, severe, and sometimes fatal encephalitis or encephalopathy associated with chickenpox or zoster in immunocompetent hosts. Most cases of encephalopathy in children after the development of chickenpox resulted from Reye's syndrome or from perivenous inflammation and demyelination (encephalomyelitis).[66,67] Encephalomyelitis was a postinfection complication that also occurred after other childhood viral exanthems.[68] In adults with zoster encephalitis, the virus was usually not found in the brain (as indicated by

inclusions or ultrastructure) unless some degree of immunosuppression, cancer, or steroid use was also present.[69]

The greatest contribution of modern diagnostic methods to our understanding of the pathogenesis of the various neurologic disorders produced by varicella–zoster virus has been the detection of the virus in large and small blood vessels of the nervous system. PCR, in situ hybridization, and immunohistochemical analyses have verified the extent to which viral infection of blood vessels causes widely variable clinical syndromes. Encephalitis from varicella–zoster virus is now recognized to be a vasculopathy that affects large or small vessels. Large-vessel arterial disease (granulomatous arteritis) occurs predominantly in immunocompetent patients, and encephalitis mediated by small vessels is found virtually exclusively in immunodeficient patients.

Large-Vessel Encephalitis (Granulomatous Arteritis)

Large-vessel encephalitis is characterized by acute focal deficit (stroke) that develops weeks or months after zoster of contralateral trigeminal distribution. A single report describes virologically confirmed large-vessel vasculopathy due to varicella–zoster virus without previous zoster.[70] Stroke results from bland[71] or, less commonly, hemorrhagic[72] infarction due to large-vessel arteritis. Disease is uncommon but not rare. Most patients are older than 60 years of age, and there is no predilection according to sex. The mean time of onset of neurologic disease is seven weeks after the development of zoster, but intervals of up to six months have been recorded. Transient ischemic attacks and mental symptoms are common, and up to 25 percent of patients die.[73]

Most patients with granulomatous arteritis have pleocytosis (usually less than 100 cells per cubic millimeter, predominantly mononuclear cells), oligoclonal bands, and increased IgG in cerebrospinal fluid. Angiography reveals focal constriction and segmental narrowing (Fig. 4), primarily in middle and anterior cerebral arteries and internal carotid arteries. Microscopical examination reveals arterial inflammation with multinucleated giant cells, varicella–zoster virus antigen, Cowdry A inclusions, and herpesvirus particles. Most recently, PCR detected varicella–zoster viral DNA in affected large cerebral arteries.[74]

Other arteries may be involved in large-vessel granulomatous arteritis. Ipsilateral occlusion of the central retinal artery occurs after zoster with a trigeminal distribution.[75] Involvement of the posterior circulation and brain-stem infarction develop after rash behind the ear[76] or on the neck,[77] and thalamic infarction occurs after rash on the tongue.[78] There is a single report of contralateral hemiplegia after zoster of thoracic distribution.[79] Afferent trigeminal ganglionic fibers innervating both intracranial and extracranial arteries[31] provide a pathway for viral spread. Because the occurrence of this condition is uncommon, controlled treatment trials have not been possible. Because the virus is present in arteries and is sometimes associated with inflammation, we recommend that patients receive acyclovir intravenously (10 to 15 mg per kilogram of body weight, three times daily for 7 to 10 days) to kill persistent virus and that they receive a short course of a steroid (60 to 80 mg of prednisone daily for 3 to 5 days) for its antiinflammatory effect.

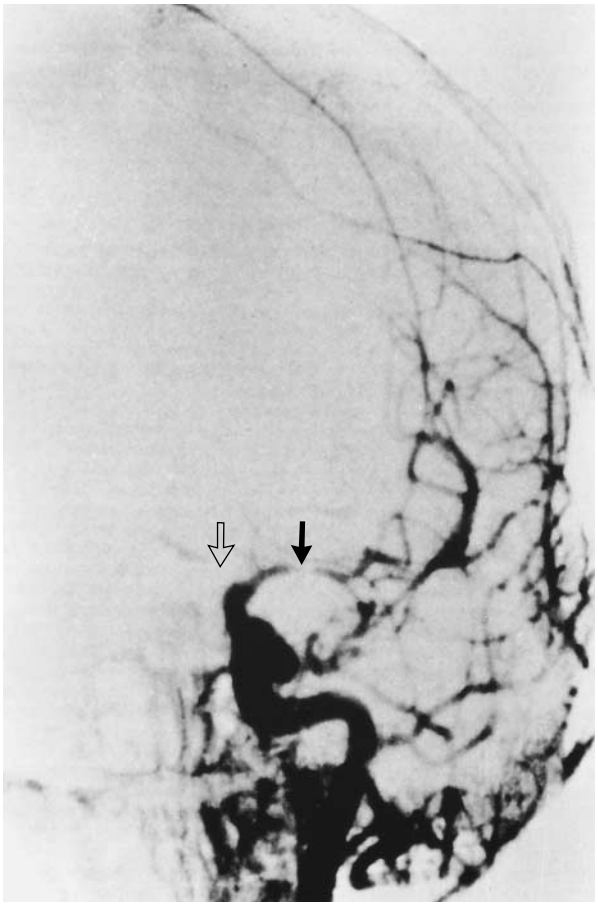

Figure 4. Cerebral Arteriogram Showing Granulomatous Arteritis in a Patient in Whom Stroke Developed in Association with Zoster Rash.

Shown are occlusion of the left anterior cerebral artery (open arrow) and focal narrowing of the proximal left middle cerebral artery (solid arrow).

Small-Vessel Encephalitis

With the current increase in the number of patients with AIDS or immunosuppression due to transplantation or cancer,[80] small-vessel encephalitis has become the most common complication of zoster that involves the central nervous system. The typical patient has had zoster weeks to months earlier, or even

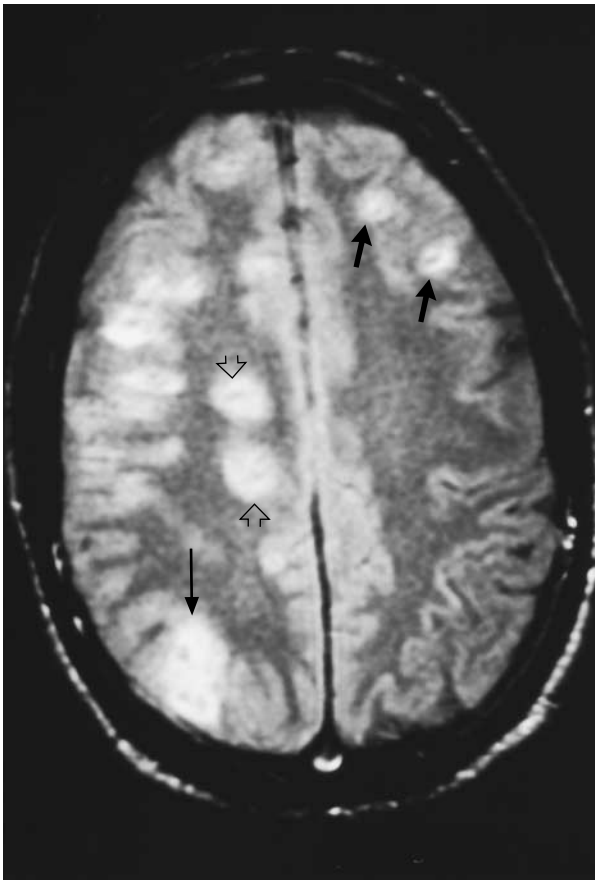

Figure 5. Magnetic Resonance Image of the Brain of a Patient with Varicella–Zoster Viral Encephalitis, or Small-Vessel Vasculopathy.

Shown are multifocal areas of infarction: a superficial wedge-shaped lesion (long solid arrow), deep ovoid lesions in white matter (open arrows), and smaller lesions at junctions of gray and white matter (short solid arrows).

recurrent zoster, followed by chronic progressive encephalitis.[81] Small-vessel disease develops more frequently without antecedent rash than does large-vessel disease. Neurologic disease (manifested by hemiplegia, aphasia, and visual-field deficits) is subacute, and death commonly occurs.

Its clinical features include headache, fever, vomiting, mental changes, seizures, and focal deficit. Magnetic resonance imaging of the brain reveals large and small ischemic or hemorrhagic infarcts, often both, of cortical and subcortical gray and white matter (Fig. 5). Deep-seated lesions in white matter, which are ischemic or demyelinative, often predominate. Demyelinating lesions in small-vessel encephalitis are smaller and less coalescent than those in progressive multifocal leukoencephalopathy.[82-84] There is usually mild mononuclear pleocytosis, a normal or elevated level of protein, and a normal level of glucose in cerebrospinal fluid.

Two reports describe hypoglycorrhachia in zoster meningoencephalitis.[85,86] In suspected cases of small-vessel encephalitis due to zoster, the cerebrospinal fluid should be studied for both varicella–zoster viral DNA (Fig. 6) and varicella–zoster virus antibody. The presence of either or both in cerebrospinal fluid in the typical clinical setting is strong presumptive evidence of small-vessel encephalitis due to varicella–zoster virus.[87] Diagnosis may be particularly difficult in patients without rash when the clinician is unaware of a history of zoster followed by the typical clinical features and multifocal lesions seen on magnetic resonance imaging of the brain.[81,88] Because disease occurs infrequently and is life-threatening, no controlled treatment trials have been conducted. We recommend empirical treatment with acyclovir (15 to 30 mg per kilogram per day) for 10 days (or longer in severely immunocompromised patients).

Ventriculitis and Meningitis

We have encountered unusual presentations of encephalitis in immunocompromised patients in whom varicella–zoster virus infected predominantly the ependyma or meninges.[84] A gait disorder and hydrocephalus with periventricular enhancing lesions developed in some patients. Necrotizing ventriculitis with preferential varicella–zoster viral infection of ependymal cells was found on autopsy. Other cases of encephalitis presented as meningoencephalitis in patients positive for the human immunodeficiency virus (HIV), with thousands of cells and grams of protein in the cerebrospinal fluid, enhancing meningeal lesions on magnetic resonance imaging (Fig. 7), and histopathological evidence of necrotizing vasculitis affecting primarily meninges. Either the brain or the spinal cord[89,90] may bear the brunt of disease.

ZOSTER SINE HERPETE

The notion of zoster sine herpete is attributable to Lewis,[91] who described patients with zoster who had dermatomal-distribution pain in areas distinct from the rash of zoster. Zoster sine herpete is currently defined as dermatomal-distribution pain without antecedent rash. Before PCR, verification was limited to serologic testing. The first documented case was in a physician who had acute pain of trigeminal distribution without rash, which was associated with a quadrupling of antibody to varicella–zoster virus but not antibody to herpes simplex virus.[92] The diagnosis was confirmed only after PCR analysis of the DNA of two men without rash who had had prolonged radicular pain of thoracic distribution. Amplifiable varicella–zoster viral DNA, but not herpes simplex virus DNA, was found in cerebrospinal fluid and blood mononuclear cells.[93] Both were treated successfully with intravenous acyclovir.

In a third virologically confirmed case, electromyography demonstrated frequent fibrillation poten-

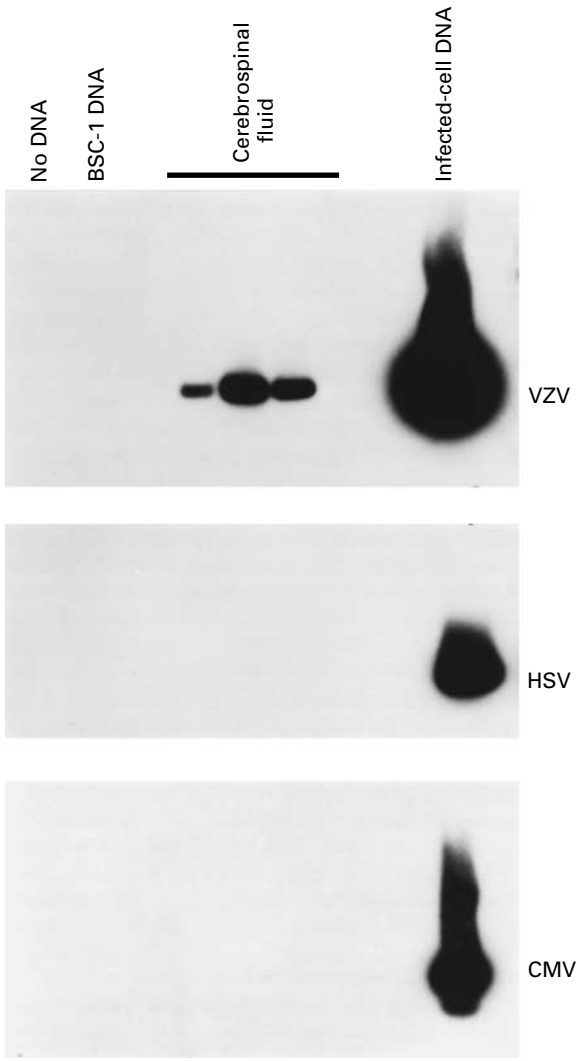

Figure 6. Varicella–Zoster Viral DNA as Shown by the Polymerase Chain Reaction in a Patient with Small-Vessel Encephalitis.

DNA was extracted from the cerebrospinal fluid of an immunocompromised patient with small-vessel vasculopathy due to varicella–zoster virus. Shown is amplifiable varicella–zoster viral DNA (indicated by the three adjacent small, dark horizontal bands) after hybridization with radioactively labeled oligonucleotides specific to varicella–zoster virus (VZV). Similar amplification and hybridization of the same cerebrospinal fluid DNA with oligonucleotides specific to herpes simplex virus (HSV) and cytomegalovirus (CMV) did not produce a signal. Positive controls were DNA from cells infected with varicella–zoster virus, herpes simplex virus, and cytomegalovirus that were amplified and hybridized (infected-cell DNA) to virus-specific probes (large dark bands at right). Negative controls were DNA from the uninfected BSC-1 line of African-green-monkey kidney cells (BSC-1 DNA) and samples without DNA.

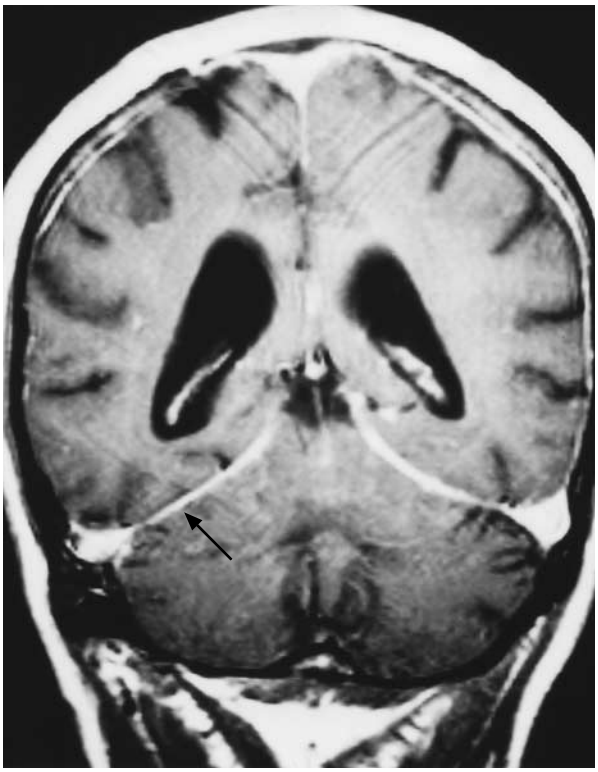

Figure 7. Magnetic Resonance Image of the Brain of a Patient with Meningoencephalitis Due to Varicella–Zoster Virus.

This fatal complication occurred in a 54-year-old man with human immunodeficiency virus infection in whom headache, confusion, and profound pleocytosis developed. On the gadolinium-enhanced magnetic resonance image of the brain, an intense signal can be seen in the meninges between the cerebrum and cerebellum, as well as in the meninges over the convexities (arrow). Acute meningoencephalitis and necrotizing vasculitis were found on autopsy.[89]

tials restricted to chronically painful thoracic roots.[94] The patient's condition did not improve after treatment with intravenous acyclovir and oral famciclovir. The prevalence of zoster sine herpete cannot be determined until virologic analysis is performed in more patients with prolonged radicular pain. Analysis should include both PCR, to amplify varicella–zoster viral DNA in cerebrospinal fluid and blood mononuclear cells, and testing for antibodies to varicella–zoster virus in cerebrospinal fluid.

PREHERPETIC NEURALGIA

The existence of ganglionitis without rash is evidenced by the presence of radicular pain preceding zoster, termed preherpetic neuralgia. There is a single report of six patients with preherpetic neuralgia. Pain preceded the rash by 7 to 100 days and was severe, burning, radicular, and located in dermatomes outside,

as well as in, the area of eventual rash.[63] Two patients ultimately had disseminated zoster that was complicated by zoster paresis and fatal encephalitis; both patients had had long-term treatment with low-dose steroids. A third case of preherpetic neuralgia developed in a patient with prior metastatic carcinoma, and a fourth developed in a patient with an earlier episode of brachial neuritis. Two other patients with preherpetic neuralgia had no underlying disease. Further documentation of preherpetic neuralgia will determine whether its apparent association with steroid therapy and serious complications is statistically significant.

OTHER VARICELLA–ZOSTER VIRAL INFECTIONS WITHOUT RASH

Aseptic meningitis due to varicella–zoster virus and acute meningoencephalitis due to varicella–zoster virus without rash have been verified by the detection of antibodies to varicella–zoster virus synthesized intrathecally.[95] Two instances of cranial polyneuritis produced by varicella–zoster virus in apparently immunocompetent men were documented by their seroconversion to varicella–zoster virus but not to multiple other human viruses.[96,97] Some cases of acute unilateral facial paralysis (Bell's palsy) that developed without rash were attributed to varicella–zoster virus (termed geniculate zoster sine herpete) on the basis of seroconversion[98]; unfortunately, the serum samples were not tested for antibodies to other human herpesviruses.

The most extreme example of varicella–zoster virus infection of the nervous system without rash was in an immunocompromised man in whom meningoradiculitis developed; he died three weeks after the onset of neurologic disease.[99] At autopsy, hemorrhagic inflammatory lesions with Cowdry A inclusions were found in meninges and nerve roots that extended from cranial-nerve roots to the cauda equina. Varicella–zoster virus (but not herpes simplex virus or cytomegalovirus) antigen and nucleic acid were detected in all infected tissue.

DIAGNOSIS OF NEUROLOGIC DISORDERS PRODUCED BY VARICELLA–ZOSTER VIRUS

PCR analysis and antibody testing of cerebrospinal fluid to confirm the role of varicella–zoster virus in producing the many varied clinical disorders affecting the peripheral and central nervous system are widely available and should be used, particularly because effective antiviral therapy exists. In the appropriate clinical setting (i.e., in patients with acute or subacute spinal cord disease, acute or chronic progressive encephalitis, or chronic radicular pain with or without rash), the presence of varicella–zoster viral DNA, antibodies to varicella–zoster virus, or both in cerebrospinal fluid is strong presumptive evidence of infection. Even the detection of antibodies in cerebrospinal fluid without the amplification of varicella–zoster viral DNA by PCR supports the diagnosis of infection of the nervous system.[87] Analysis of serum for antibodies is of no value, because antibodies to varicella–zoster virus persist in serum in nearly all adults.[100]

Unlike other acute viral encephalitides in which virus is detectable in cerebrospinal fluid early in disease and an antibody response appears days or weeks later, varicella–zoster viral infection of the nervous system is often protracted, especially in immunocompromised patients. Because it is impossible to predict from clinical information whether cerebrospinal fluid will contain viral DNA or antibody, both PCR and antibody analysis should be performed. Used together, these tests have confirmed the diagnosis of myelitis due to varicella–zoster virus,[61] large- or small-vessel encephalitis,[84] and zoster sine herpete.[93] The finding of varicella–zoster viral DNA in the cerebrospinal fluid of children with postvaricella cerebellitis is important, because cerebellar ataxia after chickenpox, previously thought to be immune-mediated, may be due to viral infection.

CONCLUSIONS

A variety of disorders of the central and peripheral nervous systems are caused by varicella–zoster virus. Modern virologic techniques have greatly increased our understanding of latency and have helped to clarify the neurologic spectrum of disease, reflecting the many cell types that the virus can infect.

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