Herpes Zoster in Older Adults

Kenneth Schmader

Center for the Study of Aging and Human Development and Division of Geriatrics, Department of Medicine, Duke University Medical Center; and Geriatric Research, Education and Clinical Center, Durham Veterans Affairs Medical Center, Durham, North Carolina

Herpes zoster (HZ) strikes millions of older adults annually worldwide and disables a substantial number of them via postherpetic neuralgia (PHN). Key age-related clinical, epidemiological, and treatment features of zoster and PHN are reviewed. HZ is caused by renewed replication and spread of varicella-zoster virus (VZV) in sensory ganglia and afferent peripheral nerves in the setting of age-related, disease-related, and drug-related decline in cellular immunity to VZV. VZV-induced neuronal destruction and inflammation causes the principal problems of pain, interference with activities of daily living, and reduced quality of life in elderly patients. Recently, attempts to reduce or eliminate HZ pain have been bolstered by the findings of clinical trials that antiviral agents and corticosteroids are effective treatment for HZ and that tricyclic antidepressants, topical lidocaine, gabapentin, and opiates are effective treatment for PHN. Although these advances have helped, PHN remains a difficult condition to prevent and treat in many elderly patients.

Herpes zoster (HZ) is a vexing neurocutaneous disease that is caused by the reactivation of varicella-zoster virus (VZV) from a latent infection of dorsal sensory or cranial nerve ganglia. VZV is a double-stranded DNA herpesvirus with a genome that contains ~125,000 base pairs and encodes ~70 gene products. Immediate early gene products regulate the expression of VZV early and late genes. Early genes encode proteins that are important in viral replication, such as virus-specific DNA polymerase and viral thymidine kinase, the enzyme that phosphorylates acyclovir and penciclovir to their active forms. Late genes encode structural nucleocapsid proteins and membrane glycoproteins that serve as targets for the immune system [1].

VZV is fascinating because it spreads from person to person, with high attack rates during the well-known childhood illness of varicella; it has the ability to establish a latent infection for the lifetime of the host; and it retains the capacity after many decades to emerge at unpredictable times to cause HZ. During latent periods, VZV appears to evade the immune system by markedly limiting the number of genes expressed during latent periods and by downregulating expression of major histocompatibility complex class I antigens on the surface of infected cells. During reactivation, VZV overwhelms immune control and spreads in the affected ganglia and sensory nerves to the skin. This event is more likely to occur in elderly people, partly because of age-related decline in specific cell-mediated immune responses to VZV. Virologists are working on the molecular mechanisms of VZV reactivation; epidemiologists have elucidated several host characteristics that affect the risk of HZ. The immunocompetent elderly host will be the focus of the information that follows.

EPIDEMIOLOGY

Epidemiological studies of HZ consistently document a sharp increase in the likelihood of contracting HZ with age. In an excellent longitudinal study done from 1947 through 1962 in Cirencester, England, Hope-Simpson [2] discovered an HZ incidence rate of 0.74 per 1000 person-years in children aged <10 years, 2.5 per 1000 person-years in adults aged 20–50 years, and 7.8 per 1000 person-years in those aged >60 years. The increased risk of having HZ with age was most recently confirmed in Boston, where investigators reported incidence rates for the following age groups: 25–34 years (1.9 per 1000 person-years), 35–44 years (2.3 per 1000 person-years), 45–54 years (3.1 per 1000 person-years), 55–64 years (5.7 per 1000 person-years), and ≥65 years (11.8 per 1000 person-years) [3].

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Reprints or correspondence: Dr. Kenneth Schmader, 182 Geriatric Research, Education and Clinical Center, Durham Veterans Affairs Medical Center, Durham, NC, 27705 (schma001@mc.duke.edu).

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The incidence of HZ increases sharply among patients aged ~50–60 years and continues an upward course in the decades >60 years. In the Duke Established Populations for Epidemiological Studies of the Elderly [4], the lifetime risk of having HZ increased significantly with age even among elderly patients (OR, 1.20 for every 5-year interval in patients >65 years old; 95% CI, 1.10–1.31). Extrapolating from HZ epidemiological studies, experts calculate the lifetime incidence rate of HZ to be 10%–20% in the general population and as high as 50% of a cohort surviving to age 85 years. Investigators estimate an annual incidence of 600,000 to 850,000 cases of HZ in the United States.

Another notable age-related feature of HZ is an increased prevalence of postherpetic neuralgia (PHN) with age. For example, Hope-Simpson [5] noted that the prevalence of pain ⩾1 months after onset of rash was 0 in age group of 0–29 years and 3%–4% in the age group of 30–49 years but 21% in the age group of 60–69 years, 29% in the age group of 70–79 years, and 34% in the age group >80 years, in England. In Boston, patients aged ⩾50 years had a 14.7-fold higher prevalence (95% CI, 6.8–32.0) of pain 30 days after onset of rash compared with patients aged <50 years [6]. Thus, not only is HZ considerably common among elderly people, but so too is chronic HZ pain. This increased incidence of HZ and PHN with age correlates with the simultaneous age-related decrease in VZV-specific cell-mediated immunity.

Cellular immune dysfunction in certain disease states is another potent trigger for HZ. The types of immunosuppressed patients at great risk for HZ include those with HIV infection, Hodgkin's disease, non-Hodgkin's lymphomas, leukemias, bone marrow and other organ transplants, systemic lupus erythematosus, and those who take immunosuppressive medications. Other potentially important risk factors include white race, psychological stress, and physical trauma [7]. Sex, marital status, educational level, season, or urban versus rural residence do not affect HZ risk. There are no controlled studies indicating that exposure of a latently infected patient to an individual with HZ or varicella causes HZ [8].

CLINICAL FEATURES

The clinical expression of HZ requires VZV replication and spread in the affected sensory ganglion and peripheral sensory nerve [9]. VZV may also reach the corresponding dorsal root and adjacent spinal cord and circulate in the blood. These events evoke a cellular immune response and neuronal inflammation, hemorrhage, and destruction of neurons. During this time, the patient experiences a prodrome of pain or discomfort in the affected dermatome. This worrisome prologue masquerades as many other painful conditions in elderly people, bewildering patients, caregivers, and physicians. One clue to the presence of VZV-induced neuronal destruction is very sensitive skin in the affected dermatome. The prodrome usually lasts a few days, although there are case reports of it lasting weeks to months.

Eventually the virus infects cells in the dermis and epidermis, produces the characteristic rash, and reveals the reason for the patient's pain. The unilateral, dermatomal rash begins as a red, maculopapular eruption, usually develops vesicles, and most commonly involves the T1 to L2 and V1 dermatomes. It is not uncommon for patients to develop lesions in adjacent dermatomes. The vesicles contain VZV. During the vesicular stage, the patient poses no threat to latently infected people but may transmit VZV to a susceptible person (usually a child) and cause varicella. Typically, the vesicles crust over in 7–10 days. During nonvesicular stages, the patient is not contagious. These simple facts can allay the worries of family and friends of patients with HZ who may avoid the patient for fear of infection. Along with the rash, most patients experience a dermatomal pain syndrome caused by acute neuritis. The neuritis is described as burning, deep aching, tingling, itching, or stabbing pain, and ranges from mild to severe.

This pain continues after the rash has healed in as many as 60%–70% of people aged >60 years and develops into PHN. In addition to older age, greater acute pain severity and rash severity are risk factors for PHN [10]. Fortunately, the number of elderly HZ patients with pain declines over weeks to months from onset of rash. In an overview of acyclovir trials, the percentage of patients aged ⩾50 years with any pain in the placebo group was 54% at 3 months and 35% at 6 months after onset of rash [11]. In some HZ studies, pain intensity and its effect on activities of daily living was not stated. Nonetheless, a substantial subset of elderly patients with HZ have a poor prognosis with respect to pain. Many of these patients are refractory to all treatments, and in some, the pain may actually get worse over time. Furthermore, some elderly patients have pain-free intervals of weeks or even months, only to note the return of their pain.

PHN is clearly the most debilitating aspect of HZ. The patient with PHN may experience constant pain (described as burning, aching, or throbbing), intermittent pain (described as stabbing or shooting), and stimulus-evoked pain such as allodynia (described as tender). Allodynia, the experience of pain after a nonpainful stimulus, is a particularly disabling component of the disease. Patients with allodynia experience severe pain after the lightest touch of the affected skin by things as trivial as a cold wind or a piece of clothing. These subtypes of pain may produce chronic fatigue, sleep disorders, depression, anorexia, weight loss, and social isolation. Furthermore, PHN can impair the elderly patient's functional status by interfering with basic activities of daily life such as dressing, bathing, and mobility

and instrumental activities of daily life such as traveling, shopping, cooking, and housework [12].

Less frequent but important complications of HZ in elderly patients, other than PHN, include the following: ocular inflammation with impaired vision in ophthalmic HZ; stroke secondary to granulomatous arteritis of the internal carotid artery in ophthalmic HZ; focal motor paresis in muscles served by nerve roots of the corresponding affected dermatome; vertigo, hearing, and facial paresis in cranial neuritis (Ramsay-Hunt syndrome); meningoencephalitis; and secondary bacterial infection of the rash.

DIAGNOSIS

HZ is instantly recognizable when an elderly patient presents with the typical dermatomal rash and pain. The main consideration in the differential diagnosis is zosteriform herpes simplex. Herpes simplex commonly recurs many times, most often affects younger adults, and usually does not generate chronic pain. Nonetheless, it may be very difficult to distinguish the 2 conditions on clinical grounds, particularly with dermatomal vesicular rashes on the buttocks and perioral area. Also, like many conditions in geriatrics, HZ may present atypically. The rash may never appear as a diagnostic guide in elderly patients with dermatomal pain alone ("zoster sine herpete"); acute facial palsy, hearing loss, vertigo, or dysgeusia (cranial neuritis); blurred vision and eye pain (acute retinal necrosis); and fever, delirium, and meningismus (meningoencephalitis).

Therefore, clinical diagnosis is sufficient in the typical case of HZ, but laboratory diagnostic testing is useful for differentiating herpes HZ from herpes simplex, for suspected organ involvement, and for atypical presentations [9]. The yield of diagnostic testing is greater in specimens from early vesicular lesions (percent sensitivity quoted below) than from late pustular or crusted lesions. Immunofluorescence antigen detection of VZV antigens in vesicle scrapings or other specimens (i.e., tissue biopsy or cerebrospinal fluid) is an excellent test because it is rapid (measured in h), specific, and sensitive (~90%). VZV culture is slower and less sensitive (~40%), but it remains a standard in making the virological diagnosis. Tzanck smears may suggest VZV infection if multinucleated giant cells and intranuclear inclusions are demonstrated in stained vesicle scrapings, but the technique cannot differentiate VZV from herpes simplex virus infections. VZV DNA detection by PCR is very sensitive (nearly 100%) and specific and is particularly useful for unusual cases or unusual specimens (i.e., only crusts available for testing). If no rash is present (i.e., suspicion of HZ sine herpete) or specimens are inadequate, then one can pursue the diagnosis serologically by use of acute and convalescent VZV IgG titers.

TREATMENT OF ACUTE HZ

The principal goal of the treatment of HZ in elderly patients is the reduction or elimination of pain. Nonpharmacological approaches to HZ pain help accomplish this goal. For example, reassurance and education about the illness dispel myths and fears about HZ. Social support, mental and physical activity, adequate nutrition, and a caring attitude go a long way toward coping with this illness. Pharmacological approaches to HZ pain include use of antiviral therapy, anti-inflammatory drugs, and analgesics.

Antiviral therapy. Acyclovir, famciclovir, and valacyclovir are guanosine analogs that are phosphorylated by viral thymidine kinase and cellular kinases to a triphosphate form that inhibits VZV DNA polymerase. In general, these drugs are safe and well tolerated by elderly patients. The most common adverse effects are nausea and/or vomiting, diarrhea, and headache in ~8%–17% of patients [14–16]. The drugs are excreted by the kidneys, and dosages must be adjusted to allow for renal insufficiency. Infection with VZV resistant to acyclovir (mediated by the lack of thymidine kinase) has been reported in patients with AIDS and in transplant patients who received prolonged acyclovir therapy, but not (yet) in immunocompetent elderly patients.

Randomized, controlled trials indicate that orally administered acyclovir (800 mg 5 times a day for 7 days), famciclovir (500 mg q8h for 7 days), and valacyclovir (1 g t.i.d. for 7 days) reduce acute pain and the duration of chronic pain in elderly patients with HZ who are treated within 72 h of the onset of rash [13]. For example, in a placebo-controlled trial of famciclovir, the median time to loss of pain was 60–63 days with famciclovir and 120 days with the placebo in patients with pain at rash healing [14]. In a study of valacyclovir versus acyclovir, the median time to cessation of pain was 38 days for valacyclovir and 51 days for acyclovir [15]. The effect of acyclovir on chronic pain is less certain because clinical trials of acyclovir versus placebo have had conflicting results with respect to chronic pain [11, 16, 17]. Unfortunately, 20%–30% of treated patients in antiviral trials had pain 6 months from HZ onset, indicating that patients who have been treated can develop PHN. Currently available data suggest that all 3 drugs are acceptable agents, and factors other than efficacy, such as cost and dosing schedule, may determine the choice.

Anti-inflammatory therapy. Two well-designed clinical trials with data on corticosteroids versus placebo in older patients with HZ showed equal rates of chronic pain in the 2 groups [18, 19]. In addition, 2 recent, well-designed clinical trials of acyclovir with or without corticosteroids demonstrated that corticosteroids added nothing to acyclovir in the prevention of PHN [19, 20]. The most common adverse effects in these trials were gastrointestinal symptoms (dyspepsia, nausea, and vomiting), edema, and granulocytosis. These data argue

against the routine use of corticosteroids in elderly patients with HZ. Interestingly, corticosteroids reduced acute HZ pain in most trials, although that beneficial effect was not sustained. In the most recent trial of acyclovir and prednisone, time to uninterrupted sleep, return to daily activity, and cessation of analgesic therapy was significantly accelerated in patients who received corticosteroids. The patients in the trial had an average age of 60 years and no relative contraindications to corticosteroids such as hypertension, diabetes mellitus, or osteoporosis [20]. Therefore, some experts advocate orally administered corticosteroids for otherwise healthy older adults with moderate to severe pain and no contraindications to corticosteroids. Prednisone was administered orally at 60 mg/day for days 1–7, 30 mg/day for days 8–14, and 15 mg/d for days 15–21. Some clinicians use corticosteroids for VZV-induced facial paralysis and cranial polyneuritis to improve motor outcomes and pain.

Analgesic therapy. Clinicians should employ analgesic therapy to reduce acute HZ pain regardless of effects on chronic HZ pain. The choice of nonopiate or opiate analgesic drugs depends on the patient's pain severity, underlying conditions, and response to the drug. The principles of excellent pain management, such as scheduled analgesia, use of standardized pain measures, and close follow-up, should be applied to acute HZ pain management, as with any other painful condition. If pain control from antiviral agents and analgesic drugs is inadequate, then regional or local anesthetic nerve blocks should be considered. Although there are no randomized controlled trials of this approach for the treatment of acute pain or the prevention of PHN, several case series have consistently reported acute pain relief from a variety of anesthetic techniques.

The effectiveness of well-managed opiates, regional anesthetic nerve blocks, anticonvulsants, and tricyclic antidepressants during the acute phase in reducing chronic HZ pain is not known but needs to be tested in rigorous clinical trials. One small study of amitriptyline or placebo during acute HZ in elderly patients found that significantly more amitriptyline recipients were pain free at 6 months but not at 1 or 3 months after onset of rash [21]. The use of acyclovir was unbalanced between the groups, and amitriptyline is a hazardous drug to use for elderly patients. These points argue against the use of amitriptyline acutely in elderly patients with HZ, but the result is interesting and deserves better study with less-toxic alternatives.

TREATMENT OF PHN

No one treatment is uniformly effective in all elderly patients with PHN. Patients and clinicians have employed a large number of treatments for PHN, but few of these treatments have been carefully evaluated. Rather than comment on all of these treatments, I will update the reader on recent clinical trials. These trials indicate that topical lidocaine, gabapentin, opiates, tricyclic antidepressants, and intrathecal methylprednisolone can significantly reduce pain in patients with PHN [22].

Topical lidocaine. The topical lidocaine patch and EMLA cream have produced significant pain relief in patients with PHN in uncontrolled and controlled clinical trials [22, 23]. The 10-cm × 14-cm lidocaine patch contains a 5% lidocaine base and other ingredients on a polyester backing. One or more patches are applied over the affected area for 12 h a day. EMLA is applied over the affected area under an occlusive dressing once a day. It may take up to 2 weeks to determine whether these treatments are effective. Systemic lidocaine toxicity has not been reported with topical lidocaine preparations. The disadvantages of the lidocaine patch are substantial cost and application site reactions such as skin redness or rash.

Gabapentin. In a randomized, placebo-controlled trial of gabapentin in PHN, the average daily pain score of treated patients declined from 6.3 to 4.2 on a 0 to 10-point pain scale compared with a decline from 6.5 to 6.0 in the placebo group ($P < .001$) [24]. Forty-three percent of the treated group rated their pain as "moderately or much improved," compared with 12% of the placebo group. Study participants received an initial dose of 300 mg, and the dose was titrated over a 4-week period to 300 mg, 600 mg, 900 mg, and 1200 mg 3 times a day or until intolerable adverse effects occurred. The adverse effects of gabapentin included somnolence (27%), dizziness (24%), and ataxia (7%). These adverse effects will limit the use of gabapentin in elderly patients with falls, disturbance of gait, and cognitive impairment.

Tricyclic antidepressants. Five randomized, controlled clinical trials of amitriptyline, 1 trial of desipramine, and 1 trial of nortriptyline demonstrated moderate to good pain relief in 44%–67% of elderly patients with PHN [12, 22]. Nortriptyline and desipramine are preferred alternatives to amitriptyline among elderly patients because they cause less sedation, cognitive impairment, orthostatic hypotension, and constipation. Given the adverse effects of amitriptyline among elderly patients and the data supporting its use, Watson et al. [25] compared amitriptyline and nortriptyline among patients with PHN in a study that used a double-blind crossover design. The 2 agents reduced pain in ~55% of patients, but nortriptyline was better tolerated. A conservative dosing regimen of nortriptyline begins with 10 mg at night and increases the dose every 4–7 days by the same amount until either reduction in pain occurs or intolerable side effects occur. At least 4 weeks of therapy is required (4–8 weeks recommended), and therapy should be continued for 3–6 months for adequate pain reduction.

Opiates. There is increasing evidence that a subset of patients with PHN respond to chronic opioid therapy. In a recent randomized, placebo-controlled, crossover trial of sustained-release oxycodone in PHN, treated patients reported significant pain relief, as measured by a visual analog scale and a numer-

ical-verbal 6-point pain scale, compared with those who received placebo [26]. A total of 67% of patients preferred oxycodone, compared with 11% of patients who preferred placebo. The initial dosage of controlled-release oxycodone was 10 mg every 12 h. The dosage was increased weekly to 20 mg every 12 h and to a possible maximum of 30 mg every 12 h. The most frequently reported adverse effects were constipation, nausea, and sedation.

Intrathecal methylprednisolone. In patients with intractable PHN >1 year who had failed to respond to the above treatments, Kotani et al. [27] randomized 270 patients to receive intrathecal methylprednisolone-lidocaine ($n = 89$), intrathecal lidocaine only ($n = 91$), or no injection (control group; $n = 90$) and measured their burning, lancinating, and allodynic pain for 2 years. Approximately 90% of the methylprednisolone-lidocaine group reported good or excellent pain relief compared with ~6% of the lidocaine-only group and 4% of the control group at 4-week, 1-year, and 2-year follow-up. The remarkable efficacy and safety of this intervention will need to be reproduced in other studies and clinical practice, but the results suggest a useful treatment for patients refractory to simpler regimens.

PREVENTION

Takahashi et al. [28] developed a live attenuated varicella-zoster vaccine in 1974 by isolating VZV from a child with varicella and passing the isolate in human embryonic lung fibroblasts and guinea pig embryo cells. Investigators have carefully studied the safety, immunogenicity, and effectiveness of the vaccine in preventing varicella in susceptible children and adults. The vaccine is safe and well tolerated, and it induces protective antibodies and cellular immunity for many years in these people. Vaccine efficacy in protection against varicella is ~85%–90%. Breakthrough varicella develops in 2%–3% of vaccine recipients each year, but the illness is mild. These encouraging results have not necessarily translated into widespread acceptance of the vaccine. Nonetheless, many countries have licensed the vaccine for the prevention of varicella. At least 25 states in the United States require vaccination for entry into school or day care, and health care workers have administered millions of doses worldwide. In the United States, >20 million doses have been administered, and VZV epidemic curves have been reduced in regions where the vaccine is accepted.

How will primary prevention of varicella with the varicella-zoster vaccine affect the incidence and natural history of HZ? The answer to this question will require decades of observation. The ideal scenario envisions a marked decline in the incidence of HZ and PHN as the cohorts of children who are now receiving the vaccine enter older adulthood. This scenario assumes widespread vaccination of immune-naïve people, which is not necessarily occurring in many countries. Furthermore, the vaccine virus does establish a latent infection that can reactivate to cause HZ. However, vaccine virus–associated HZ will probably be much less frequent and severe in older adults than natural HZ because the vaccine virus is highly attenuated. Some experts speculate that the incidence of HZ could increase, at least in the near future, as varicella incidence declines. They reason that a decline in the incidence of varicella will reduce the population's exposure to VZV, prevent subsequent immune boosting to VZV, and increase the risk of VZV reactivation.

In the meantime, hundreds of millions of latently infected older adults worldwide are at risk for HZ for the foreseeable future. Given that cellular immunity to VZV declines with age, might vaccination of latently infected elderly persons with the varicella-zoster vaccine prevent HZ or PHN? An effective vaccine would be a useful intervention because currently there is no way to prevent HZ, and therapies of acute HZ and PHN are only partially effective. The vaccine induces significant increases in mean anti-VZV antibody levels, IFN-γ production, T cell proliferation indexes, cytokine secretion, and VZV-specific T cell responder frequency in elderly adults. Levin et al. [29] reported that, 6 years after vaccination, VZV responder cell frequency was still significantly improved over baseline in 130 patients who were aged 55–87 years at the time of vaccination. Furthermore, the vaccine has been well tolerated by elderly people; minor, transient injection site reactions were the most common adverse event. A randomized, double-blind, placebo-controlled Veterans Affairs Cooperative Studies Program trial is in progress in the United States to evaluate the effects of a more potent formulation of the vaccine on HZ and PHN in elderly people.

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