Herpes Zoster in the Elderly: Issues Related to Geriatrics

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This article reviews specific clinical and research issues of herpes zoster related to geriatric medicine. Salient epidemiological and clinical issues include the increasing probability of zoster and postherpetic neuralgia with aging, age-related decline in immunity to varicella-zoster virus, the functional and psychosocial impact of zoster on the quality of life of the elderly, illness behavior in elderly patients with zoster, and varicella-zoster virus transmission and control in the nursing home. The role of antiviral therapy, corticosteroids, and analgesics; the measurement and analysis of pain, health-related quality of life, and functional status; and development of the varicella vaccine in the management of zoster in the elderly are also emphasized. Fertile research opportunities exist within these areas for investigators interested in infectious diseases, geriatrics, and other zoster-related disciplines.

Herpes zoster afflicts up to 600,000 persons in the United States each year and causes substantial suffering among elderly individuals [1]. Increasingly large numbers of persons are experiencing the disease, owing to population aging and increasing numbers of immunosuppressed hosts. The purpose of this presentation is to review specific issues of herpes zoster related to geriatrics and to emphasize potentially fruitful areas of research collaboration between infectious diseases specialists and geriatricians. The review will begin with a description of the presentation of a patient seen in the Duke Geriatric Evaluation and Treatment Clinic 5 years after the onset of zoster.

Patient Presentation

The patient, a 70-year-old man, was in excellent health until the acute onset of a “terrible” pain in his right upper abdomen and lower chest. The pain was initially diagnosed as cholecystitis, but diagnostic testing revealed no gallstones. The cause of the pain remained elusive until 4 days after onset of rash, when he visited the emergency department because of ongoing pain. While helping him remove his shirt for the examination, a nurse pointed out a red, blistering rash located on his right back in the T5 dermatome and told him he had shingles. The emergency department physician confirmed the diagnosis, treated him with meperidine, and sent him home with codeine and acyclovir. The rash healed over the next 3 weeks, but he noticed minimal relief from the acute pain.

The patient has experienced severe postherpetic neuralgia (PHN) for 5 years now and seeks relief. He describes a constant deep aching that is punctuated by sharp pains and involuntary muscle contractions in the area of the affected dermatome. In addition, he complains bitterly about extremely sensitive skin in the affected dermatome and is unable to wear clothes over the area. Over the years, he has tried codeine, oxycodone, morphine, amitriptyline, amitriptyline-perphenazine, topical lidocaine, capsaicin, mexiletine, phentoyin, carbamazepine, non-steroidal antiinflammatory agents, cyclobenzaprine, transcutaneous electrical nerve stimulation, acupuncture, epidural anesthetic/steroid injections, and intercostal nerve blocks, all without relief.

Two years after the onset of rash, while taking mexiletine and amitriptyline, he developed “grogginess” and poor balance, resulting in a subsequent fall and hip fracture, necessitating a total hip replacement. His PHN interferes with dressing, bathing, grooming, traveling, ability to concentrate, and sleeping. He and his wife go out of the house on social occasions very infrequently. He was still working as an automobile mechanic at the time of the onset of zoster, but the illness forced him to retire.

This patient’s pain is what makes zoster such a feared condition among elderly persons and what we seek to treat and prevent in the elderly. The case illustrates several key clinical features of zoster and PHN in the elderly. The acute phase of the illness was characterized by a confusing prodrome and misdiagnosis and then the ease of diagnosis once the rash appeared. The chronic phase shows the character and impact of PHN. PHN victims experience spontaneous, constant aching or burning and/or intermittent shocklike pains. In addition,
many patients experience disabling allodynia, or pain brought on by an innocuous stimulus, in the affected dermatome. Unfortunately, a subset of PHN patients not only do not respond to treatment but also suffer from adverse drug effects, a major problem in geriatric medicine.

The physical, psychosocial, and functional impact of acute and chronic zoster pain in the elderly—the fatigue, insomnia, depression, social withdrawal, and reduced ability to perform basic and instrumental activities of daily living—typifies the problems that patients, family, and clinicians face with any serious illness that affects the elderly [2]. The ultimate impact of zoster in serious cases such as this one depends on the physiological reserve of the elderly patient. In the well elder, it profoundly lowers quality of life; in the frail elder, these changes can induce a downward spiral to loss of independence and life.

**Epidemiology**

Herpes zoster is caused by the reactivation of varicella-zoster virus (VZV) from a latent state in dorsal sensory and cranial ganglia. VZV reactivation and the incidence of zoster increase so strikingly with age that the majority of zoster cases worldwide occur in the elderly [3]. Why are the elderly so vulnerable to developing zoster? The answer, in part, is thought to be immunosenescence. Cellular immune dysfunction is a very important risk factor for zoster, particularly in patients with hematologic malignancies, patients with AIDS, and patients receiving immunosuppressive therapies [4]. Furthermore, investigators have demonstrated a significant age-related decline in the number and function of T cell responders to VZV. Miller first demonstrated that the proliferative response of these cells to VZV antigen in vitro was significantly less in the elderly [5]. Berger et al. confirmed age-related differences in VZV antigen-dependent lymphocyte proliferation by demonstrating a low or absent stimulation index in lymphocytes from 33 (33%) of 100 healthy elderly persons and 0 of 43 persons aged 20–40 years [6].

Burke et al. studied lymphocyte proliferation and skin test reactivity to VZV antigen in 157 healthy, latently infected subjects of all ages and found that mean stimulation indices declined significantly by decade and that the percentage of positive skin test responses to VZV progressively declined, from 89% of 30–40-year-olds to 8% of 70–80-year-olds [7]. Finally, Hayward and Herberger showed that the frequency of VZV-responsive lymphocytes (responder cell frequency; mean ± SD) is significantly lower in the elderly (1/78,000 ± 6,600) than in younger individuals (1/14,300 ± 2,000) [8]. However, whether this apparent age-related decline is cause or coincidence has not been determined, since these cross-sectional studies have been small and investigators have not identified an immunologic correlate of zoster. Moreover, researchers now have more sophisticated tools and a greater understanding of immunology since these studies were published. The immunology of zoster and aging is a rich area for further investigation.

Another important area of development is clinical and molecular epidemiologic studies of risk factors for zoster. For example, we determined if there were racial differences in the lifetime occurrence and incidence of herpes zoster in the Duke Established Populations for Epidemiologic Studies of the Elderly, a probability sample of community-dwelling persons older than 64 years in North Carolina. After controlling for age, cancer, and demographic factors, we found that blacks were four times less likely than whites (adjusted OR, 0.25; 95% CI, 0.18–0.35; \( P = .0001 \)) to have had zoster in their lifetime, and blacks were significantly less likely to develop incident cases of zoster in 6 years of follow-up (adjusted risk ratio [RR], 0.35; 95% CI, 0.24–0.51; \( P < .001 \)) [9, 10]. The reasons for these significant racial differences remain unclear but may involve racial differences in onset of primary infection, in reexposure to VZV throughout life, or in immunity to VZV [11].

Malignancy is common in elderly persons and has an important relationship with zoster. Hodgkin’s disease, non-Hodgkin’s lymphomas, and leukemias pose a high risk for zoster [12, 13]. Patients with solid tumors are at lesser risk for zoster, but treated patients with lung, breast, or gynecologic cancers of any age were more likely to have zoster than patients with other solid tumors in one study [13]. Conversely, zoster is not a risk factor for cancer, so the presence of zoster in an elderly patient should not by itself initiate a search for a presumed underlying malignancy [14].

**Clinical Issues**

The first symptom of zoster is usually pain or abnormal sensations in the affected dermatome before the rash appears. Without this diagnostic marker, elderly patients are often exposed to unrevealing diagnostic tests and a host of misdiagnoses. One clue to incipient zoster before the rash appears is tender or sensitive skin in the affected dermatome. Zoster should be in the differential diagnosis of any acute, dermatomal pain syndrome in the elderly.

After days to weeks of this painful prodrome, the characteristic erythematous, maculopapular and then vesicular, dermometer rash erupts, and zoster usually becomes easy to diagnose. The diagnosis should be made as early as possible because antiviral therapy must be initiated within 72 hours of the onset of rash to enhance the likelihood of a successful outcome. However, elderly patients may delay coming to the doctor because they underestimate the problem, fear the diagnosis or its consequences, do not appreciate the rash, are socially isolated, or avoid the health care system. This type of illness behavior is common in elderly persons and is termed under-reporting of symptoms in the geriatric literature [15]. Ageism, fear, cognitive impairment, and barriers to health care are typical reasons for this phenomenon.
Once it is diagnosed, elderly patients and family members may harbor significant concerns about the illness. One concern is that the patient will cause zoster or chickenpox in family or friends. The vesicles do contain cell-free virus, which can be transmitted to other individuals via direct contact or the airborne route. Uninfected individuals may develop varicella after exposure to a vesicular zoster rash, so individuals with no history of chickenpox or known to be seronegative should avoid close contact with the individual until the rash has crusted over [16]. This recommendation is important in the nursing home or hospital, where caregivers are often women of child-bearing age. However, there is no convincing evidence that zoster patients cause zoster or chickenpox in latently infected seropositive individuals, who constitute >95% of the adult population.

Another obvious concern is PHN. The most common definitions of PHN are pain 1 or 3 months after the onset of the zoster rash or pain after the rash has healed. Regardless of exact definition, PHN is highly age-related. For example, pain 1 month after rash onset occurred in 10% of untreated zoster patients <40 years old and 68% of those >60 years old in one large study [17]. Furthermore, pain lasting >1 year occurs in <5% of young individuals, whereas it occurs in up to 48% of persons >70 years old [18]. Why are the elderly so vulnerable to development of PHN? The answer to this question remains an enigma and another area in need of investigation [19, 20]. Other much less common but devastational complications of zoster in the elderly include loss of vision with ophthalmic zoster, facial or limb paresis, encephalitis, hepatitis, and pneumonia.

Management

The principal reason to treat elderly patients with zoster is the reduction or elimination of pain and disability. The optimal measurement and analysis of pain in elderly patients and of the impact of zoster on health-related quality of life and functional status have been subjects of considerable debate and require ongoing research [21, 22]. Nonetheless, pain has been the focus of recent clinical trials with three agents that have activity against VZV: acyclovir, famciclovir, and valacyclovir. All three drugs reduce acute pain and may reduce duration of chronic pain when used within 72 hours of the onset of rash [18]. Oral acyclovir (800 mg five times a day) also reduces ocular complications in ophthalmic zoster, and intravenous acyclovir (10 mg/kg every 8 hours) is effective in treating visceral or CNS complications in the immunosuppressed host. Its disadvantages are poor oral bioavailability, a five-times-a-day dosing schedule, and conflicting data regarding its effect on PHN [18, 23–25].

Famciclovir has better bioavailability than acyclovir, is used in a three-times-a-day dosing regimen, and significantly reduced the duration of zoster pain (compared to that with placebo) in a randomized, controlled trial that included elderly participants. In patients with PHN, as defined as pain at rash healing in this trial, the median time to loss of pain was 63 days with famciclovir (500 mg three times a day) and 120 days with placebo (P = .02) [26]. Famciclovir has not been approved by the U.S. Food and Drug Administration for ophthalmic zoster or for the immunosuppressed host.

Valacyclovir, which is used in a three-times-a-day dosing regimen, has better bioavailability and reduced the duration of zoster pain (in comparison to that with acyclovir) in a large randomized, controlled trial in the elderly. The median time to loss of pain from zoster onset in this trial was 38 days for valacyclovir (1 g three times a day) and 51 days for standard doses of acyclovir [27]. It can be used in ophthalmic zoster but not in the immunosuppressed host, on the basis of case reports of hemolytic-uremic syndrome in association with the drug.

Remarkably, elderly patients tolerate these drugs very well, experiencing nausea, diarrhea, and headache 5%–15% of the time. On the basis of current data, it is difficult to say whether one agent is clearly superior to the other or that they uniformly prevent PHN. Unfortunately, treated patients may develop persistent zoster pain, possibly because several days of viral replication and inflammation have taken place by the time the patient reaches the doctor.

Corticosteroid drugs, in many forms, have been used by clinicians for years in attempts to reduce the inflammation and pain of zoster. However, doubts about corticosteroids have centered around ineffectiveness in preventing PHN, potential dissemination of VZV, and adverse effects, particularly in the frail elderly. Three well-designed randomized, controlled trials in the past 10 years showed no significant differences in the incidence or duration of PHN in steroid-treated patients (compared with those in placebo or acyclovir recipients), with or without the concomitant use of acyclovir [24, 28, 29]. The median age of patients in these studies ranged from 60 to 65 years, and they were excluded if they had diabetes mellitus, hypertension, osteoporosis, or cancer, which are common conditions in elderly patients. Their results argue against the routine use of corticosteroids in elderly patients with zoster. However, it should be noted that corticosteroids reduced acute pain in these studies. In addition, Whitley et al. found that the time until uninterrupted sleep, return to usual activity, and reduction of analgesic use were achieved was significantly shorter in the corticosteroid-treated group [29].

Infection control in the nursing home or hospital is an important zoster-related issue. Seronegative nursing home and hospital staff should avoid contact with the zoster patient until the rash has crusted over, to avoid varicella. The U.S. Centers for Disease Control and Prevention recommend a private room and standard precautions for immunocompetent hospitalized patients with localized zoster, to protect susceptible staff members and patients [16]. In addition to standard precautions, they recommend a private room with negative-pressure ventilation and airborne and contact precautions for immunocompromised patients with localized zoster or any patient with disseminated zoster. Similar measures are advocated for zoster patients in...
nursing homes, but they are difficult to achieve because of the limited staffing and resources of these facilities.

We have made significant strides in attacking the problem of herpes zoster, but we still seek more effective treatment and prevention of chronic zoster pain in the elderly. What strategies are worthy of investigation and collaboration between clinicians and researchers in infectious diseases, geriatrics, and other zoster-related disciplines? One strategy is the development of improved antiviral agents, searching for more potent VZV activity, better pharmacokinetics, and perhaps agents with a different mechanism of action. The most cost-effective use of current agents is also important.

Another underinvestigated area is proper pain management during acute zoster. On the basis of animal model findings and human data, pain investigators hypothesize that ongoing painful neural input during the acute inflammatory stage can cause CNS changes that generate chronic neuropathic pain [30]. The effect of carefully managed opiates, tricyclic antidepressants, and regional anesthetic nerve blocks on reducing acute pain and the duration of chronic zoster pain is an interesting area of inquiry and practice.

Finally, the varicella vaccine is an exciting possibility as an intervention in preventing zoster or PHN in elderly persons. The vaccine does significantly increase VZV responder-cell frequency, IFN-γ, and VZV IgG antibody in latently infected elderly individuals for several years, but its efficacy in zoster is unknown [31]. Clinical trials of the vaccine in the elderly are planned in Europe and the United States for the coming years. These strategies hold the promise of vanquishing zoster pain and making the misery of the patient presented in this paper an unusual occurrence rather than a common one.

References