Clinical and immunologic features of recurrent herpes zoster (HZ)

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Background: Recurrent herpes zoster (HZ) is thought to be rare, but there have been few large-scale studies of recurrent HZ.

Objective: We conducted a large-scale prospective cohort study to characterize recurrent HZ.

Methods: We examined 12,522 participants aged 50 years or older in Shozu County and followed them up for 3 years. We compared the incidence of HZ and postherpetic neuralgia, severity of skin lesions and acute pain, cell-mediated immunity, and varicella-zoster virus–specific antibody titer between primary and recurrent HZ.

Results: A total of 401 participants developed HZ: 341 with primary HZ and 60 with recurrent HZ. Skin lesions and acute pain were significantly milder and the incidence of postherpetic neuralgia was lower in patients aged 50 to 79 years with recurrent HZ than in those with primary HZ. Varicella-zoster virus skin test induced a stronger reaction in patients aged 50 to 79 years with recurrent HZ than in those with primary HZ.

Limitations: Information on previous HZ episodes was self-reported by participants, so it could not be confirmed that they actually had a history of HZ.

Conclusion: Recurrent HZ was associated with milder clinical symptoms than primary HZ, probably because of stronger varicella-zoster virus–specific cell-mediated immunity in the patients with recurrence. (J Am Acad Dermatol 2016;75:950-6.)

Key words: cell-mediated immunity; humoral immunity; large-scale community-based prospective cohort study; primary herpes zoster; recurrent herpes zoster; varicella-zoster virus.

Varicella-zoster virus (VZV) causes varicella in childhood as a primary infection.[1,2] After infection occurs, VZV remains latent in the sensory nerve ganglia throughout the lifetime of the host, with reactivation caused by impairment of immunity, aging, or stress resulting in herpes zoster (HZ).[3] Recurrent HZ is generally thought to be rare and to be limited to immunocompromised patients. Although the plausibility, actual occurrence, and frequency of recurrent HZ have been debated,[4-8] there have been few large-scale studies examining recurrent HZ. Recently, we carried out a large-scale community-based prospective cohort study on HZ.[9-14] In the current study, we analyzed data obtained from this

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cohort study over the entire follow-up period of 3 years to explore the characteristics of recurrent HZ in comparison with primary HZ. We found that recurrent HZ was characterized by less severe skin lesions, less severe pain, and a lower risk of postherpetic neuralgia (PHN) than primary HZ in the age group 50 to 79 years.

METHODS

Study design

The study design was reported previously.[9] Briefly, 12,522 Japanese persons aged 50 years or older in Shozu County were enrolled in this study on October 1, 2008. Among them, 5683 participants underwent a VZV skin test at registration. Participants were followed up for 3 years by telephone interview every 4 weeks. If they developed possible HZ, the participants attended hospitals or clinics in Shozu County registered with this study where their symptoms, severity of pain, and humoral immunity were evaluated. Photographs of skin lesions were also taken for later assessment, and samples of vesicles and crusts were collected for detection of VZV by polymerase chain reaction (PCR). All of the participants who developed possible HZ were examined by PCR and serologic testing. Cases were confirmed by the clinical evaluation committee of Nara Medical University School of Medicine in Japan, consisting of 3 dermatologists with expertise in HZ, and the final diagnosis was based on symptoms together with the results of PCR and serologic tests.

Statistical analyses were performed on the participants who developed HZ during the 3-year follow-up period, after excluding 6.4% who withdrew from the study, were lost to follow-up, or died during the study. This study was approved by research ethics committee in Nara Medical University School of Medicine.

Diagnosis of recurrent HZ

A diagnosis of recurrent HZ was made in subjects who met the following criteria: (1) a previous episode of HZ before this study, and (2) diagnosis of HZ during the study period based on symptoms combined with the results of PCR and serologic tests.

VZV skin test

To evaluate sensitivity to VZV and the level of cell-mediated immunity (CMI), we used the VZV antigen Biken (a commercially available reagent from the Research Foundation for Microbial Diseases of Osaka University, Japan). The VZV skin test antigen was licensed in Japan in 1990.[15,16] In brief, to perform this test, culture fluid of MRC-5 cells infected with VZV (Oka parental strain) was harvested and centrifuged. Then the supernatant was collected and concentrated by ultrafiltration for storage as a bulk preparation, mainly consisting of VZV glycoproteins (III and IV). The VZV glycoprotein content was evaluated by enzyme-linked immunosorbent assay (ELISA). We injected 100 μL of VZV skin test antigen intradermally into the forearm of each participant at registration. Erythema and edema were evaluated 48 hours after the injection, and the longest diameter was measured as the test result. The extent of edema was also assessed by palpation with the index finger.[17]

CAPSULE SUMMARY

- Recurrent herpes zoster (HZ) has not been well characterized.
- Symptoms of recurrent HZ were significantly milder than those of primary HZ.
- Relatively strong cell-mediated immunity against varicella-zoster virus might contribute to less severe symptoms in patients with recurrent HZ.

Assessment of humoral immunity for VZV

Blood samples were obtained from participants who developed HZ during the follow-up period to assess humoral immunity. Serologic tests for VZV antibodies, such as the neutralization test, immunoadherence hemagglutination test, and glycoprotein ELISA, were performed as described previously.[17-22] The glycoprotein ELISA was performed by using microtiter plates coated with purified VZV glycoproteins to determine the titer of IgG antibodies against viral glycoproteins. The neutralization test for VZV was done by the plaque reduction technique, with the neutralizing antibody titer corresponding to a 50% reduction in plaque count, whereas the immunoadherence hemagglutination test for VZV antibodies was based on fixation of complement by antigen-antibody complexes.

Evaluation of HZ skin lesions

Initial evaluation of subjects with possible HZ was done by physicians in Shozu County using a standard survey form that we developed. The clinical diagnosis was confirmed by the dermatologists using photographs of skin lesions. The following variables were also assessed: the presence of underlying diseases, immunosuppressant/antineoplastic therapy, date of onset of the rash, distribution of the rash, properties of the rash (erythema; number of vesicles, pustules, erosions, and crusts; and ulceration and fusion of vesicles), date of onset of pain, and