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# 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.<sup>1,2</sup> 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).<sup>3</sup> 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,<sup>4-8</sup> there have been few large-scale studies examining recurrent HZ. Recently, we carried out a large-scale community-based prospective cohort study on HZ.<sup>9-14</sup> 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.<sup>9</sup> 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.<sup>15,16</sup> 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  $\mu$ L 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.<sup>17</sup>

### 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.<sup>17-22</sup> 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

## 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.

**Abbreviations used:**

CMI:	cell-mediated immunity
ELISA:	enzyme-linked immunosorbent assay
HZ:	herpes zoster
PCR:	polymerase chain reaction
PHN:	postherpetic neuralgia
VZV:	varicella-zoster virus

other associated symptoms (eg, fever, headache, generalized HZ, multidermatomal HZ, eye complications, motor paralysis, Ramsay Hunt syndrome). We developed a clinical severity score for HZ skin lesions in which scores from 0 up to 3 points were assigned for each of the following criteria: the percentage of erythema in the lesional dermatome (score: 0-3); the number of vesicles, pustules, erosions, or crusts (score: 0-3); the presence or absence of fusion of vesicles (score: 0 or 1); the presence or absence of ulcer formation (score: 0 or 1); the number of lesional dermatomes (score: 0 or 1); and the presence or absence of generalized eruptions (score: 0 or 1). The severity score for HZ skin lesions was calculated as the sum of each of these scores at the peak of disease activity with a maximum possible score of 10, as described previously.<sup>12,13</sup> Please see the Supplementary Data, available at <http://www.jaad.org>.

**Evaluation of zoster-associated pain**

The severity of pain was evaluated by using a face scale from 0 (no pain) to 5 (pain disturbing sleep)<sup>12</sup> on days 0, 1, 2, 3, 4, 5, 6, 13, 20, 27, 34, 41, 48, 55, 85, 115, 145, and 175 after the initial medical consultation. Some patients with early resolution of pain were only followed up until day 7 after the pain disappeared. The severity score for zoster-associated pain was calculated as the area under the curve of pain versus time during the 12-week period after the onset of HZ rash. We identified patients with PHN by conducting telephone interviews once every 4 weeks for each study participant who developed HZ. A diagnosis of PHN was made in patients with either: (1) zoster-associated pain for at least 3 months after the onset, or (2) recurrence of zoster-associated pain after 3 months or longer.

**Statistical analysis**

Analysis of covariance was used to compare the severity of skin lesions, and zoster-associated pain between subjects with primary or recurrent HZ. Logistic regression analysis was used to compare the risk of PHN and the VZV skin test reaction between primary and recurrent HZ.

**RESULTS****Characteristics of the study population**

Among 12,522 participants (aged  $\geq 50$  years), 401 developed HZ: 341 with primary HZ and 60 with recurrent HZ (Table I). The 341 patients with primary HZ were 121 men and 220 women (median age 69.4 years), comprising 59 patients aged 50 to 59 years, 92 patients aged 60 to 69 years, 113 patients aged 70 to 79 years, and 77 patients aged 80 years and older. Malignancies were reported in 19 patients and 20 patients were on immunosuppressive therapy (Table I). The patients with 60 recurrent HZ were 18 men and 42 women (median age 70.1 years), comprising 9 patients aged 50 to 59 years, 16 patients aged 60 to 69 years, 21 patients aged 70 to 79 years, and 14 patients aged 80 years and older. Malignancies were reported in 2 patients and 3 patients were on immunosuppressive therapy (Table I). The characteristics of all subjects with primary or recurrent HZ are summarized in Table I. There were no significant differences of age or most other characteristics between the subjects with primary or recurrent HZ. The incidence of primary HZ was significantly higher in women than in men (OR, 1.542; 95% CI, 1.234–1.927;  $P < .001$ ), whereas there was no significant gender difference in the incidence of recurrent HZ (Table I).

**Less severe skin lesions in recurrent HZ**

Using the highest skin lesion score obtained during the course of HZ as the severity score for each subject, the average scores in each age group were compared between primary and recurrent HZ (Fig 1, A). The severity score was lower for recurrent HZ than primary HZ in the patients aged 70 to 79 years ( $P < .001$ ), but not in the other age groups (Fig 1, A). When the 3 younger age groups (50-59, 60-69, and 70-79 years [50-79 years]) were combined for comparison, patients with recurrent HZ exhibited less severe skin lesions than those with primary HZ ( $P < .001$ ) (Fig 1, B). However, no significant difference was observed between primary and recurrent HZ in patients aged 80 years and older (Fig 1, B).

**Less severe zoster-associated pain in recurrent HZ**

Next we evaluated zoster-associated pain in the acute and subacute stages of the disease. Similar to the findings for skin lesions (Fig 1), acute and subacute zoster-associated pain was significantly less severe in recurrent HZ than primary HZ in patients aged 70 to 79 years (Fig 2, A) ( $P < .001$ ) and those aged 50 to 79 years (Fig 2, B) ( $P < .001$ ).

**Table I.** Characteristics of patients with primary and recurrent herpes zoster

Group	No. of subjects	Person-years	No. of patients with HZ	Patient background factors								
				HZ incidence/y	Median age, y	Sex	VZV skin test		Acute phase VZV antibody titer			
							Immunosuppression	Diameter of erythema, mm, ±SE	Patients with edema (≥10 mm)	Glycoprotein-ELISA (log10) ±SE	NT, (log2) ±SE	IAHA, (log2) ±SE
Primary HZ	10,530	31,015	341	1.10% (M 0.84%; F 1.33%)*	69.4	M (n = 121); F (n = 220)	Malignancy (n = 19); immunosuppressive therapy (n = 20)	8.03 ± 0.66 n = 139	9.46% <sup>†</sup> n = 148	3.77 ± 0.05 n = 60	5.37 ± 0.19 n = 60	5.68 ± 0.20 n = 59
Recurrent HZ	1992	5917	60	1.01% (M 0.91%; F 1.07%)*	70.1	M (n = 18); F (n = 42)	Malignancy (n = 2); immunosuppressive therapy (n = 3)	10.11 ± 1.83 n = 31	21.88% <sup>†</sup> n = 32	3.85 ± 0.11 n = 10	5.28 ± 0.40 n = 10	5.70 ± 0.45 n = 10

HZ, Herpes zoster; F, female; IAHA, immunoadherence hemagglutination; M, male; NT, neutralization test; VZV, varicella-zoster virus.

\*The incidence of primary HZ was significantly higher in women than in men.

†The percentage of patients with edema in the skin test was significantly higher in recurrent HZ than primary HZ.

**PHN less likely in recurrent HZ**

There was a significantly lower incidence of PHN in recurrent HZ than primary HZ in patients aged 50 to 79 years (OR, 0.199; 95% CI, 0.047-0.852; *P* = .03), but not in those aged 80 years or older (Fig 3).

**Stronger VZV skin test reaction with more edema in recurrent HZ**

From among 5683 participants who underwent a VZV skin test at registration, we extracted the data of participants who developed HZ. There was no significant difference of the erythema response in the skin test between subjects with primary and recurrent HZ (Table I). The diameter of erythema tended to be larger in patients aged 50 to 79 years with recurrent HZ (mean ± SE: 11.44 ± 2.01 mm) than in those with primary HZ (mean ± SE: 8.69 ± 0.71 mm), but the difference was not significant. On the other hand, the percentage of patients with edema (≥10 mm) in the skin test was significantly higher in recurrent HZ than primary HZ when patients aged 50 to 79 years were compared (OR, 3.05; 95% CI, 1.076-8.627; *P* = .036) (Fig 4).

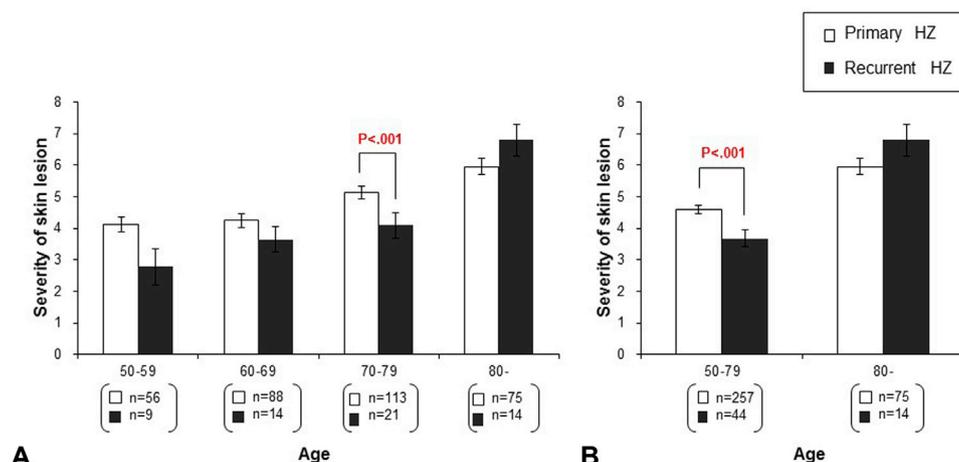
**Similar VZV-specific humoral immunity in primary and recurrent HZ**

We compared serum levels of VZV antibodies between primary and recurrent HZ. Participants who developed HZ during this study were examined for antibodies at the initial medical consultation. To minimize the effect of VZV reactivation on antibody titers, we only included patients with HZ who presented within 2 days after the onset of rash. The serum VZV antibody titers determined by glycoprotein ELISA, neutralization, and immunoadherence hemagglutination test results did not differ between the primary and recurrent HZ groups (Table I), suggesting that the risk of developing recurrent HZ might not depend on the humoral immune status.

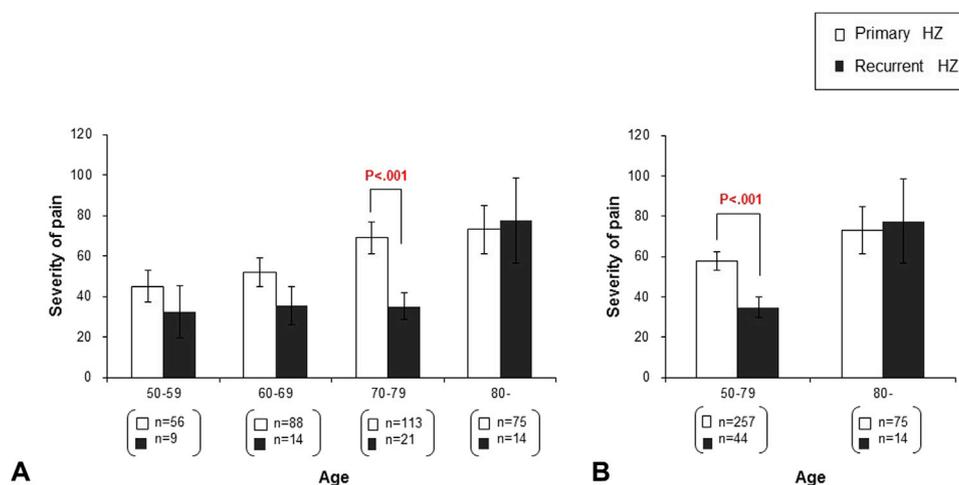
**DISCUSSION**

Among the 12,522 participants investigated in this study, 401 participants developed HZ, including 341 with primary HZ and 60 with recurrent HZ. The annual incidence of primary HZ was 1.10%, whereas that of recurrent HZ was 1.01%.

We showed that patients with recurrent HZ aged 50 to 79 years developed less severe skin lesions, had less severe acute pain, and had a lower risk of PHN than patients with primary HZ of the same age group, whereas these differences were not noted in patients aged 80 years and older. These findings may be related to stronger CMI in patients with recurrent HZ than in patients with primary HZ, because the VZV skin test induced more edema and tended to induce



**Fig 1.** Severity of skin lesions between primary and recurrent herpes zoster (HZ) in each age group (A) and in 2 age groups (50-79 vs  $\geq 80$  years) (B). Bars indicate the mean severity scores adjusted for sex (error bars, SEM).



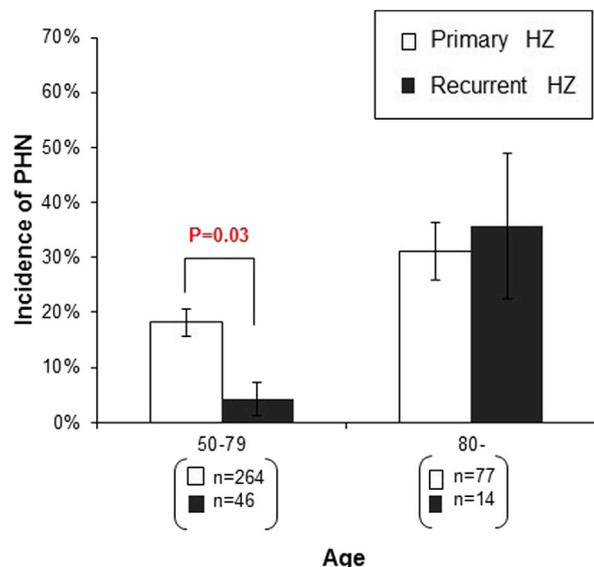
**Fig 2.** Severity of acute and subacute zoster-associated pain between primary and recurrent herpes zoster (HZ) in each age group (A) and in 2 age groups (50-79 vs  $\geq 80$  years) (B). Bars indicate the mean severity scores adjusted for sex (error bars, SEM).

a larger area of erythema in the patients with recurrent HZ aged 50 to 79 years than in those with primary HZ. The VZV skin test used in the current study does not cause the typical induration that is commonly induced by the tuberculin skin test, but instead induces edema accompanied by erythema. Okuno et al<sup>11</sup> reported that the diameters of edema and erythema induced by the VZV skin test were inversely correlated with the incidence of HZ. In contrast, there was no significant difference of VZV-specific humoral immunity between primary HZ and recurrent HZ. These results suggest that the clinical differences between primary HZ and recurrent HZ may be more dependent on CMI than humoral immunity.

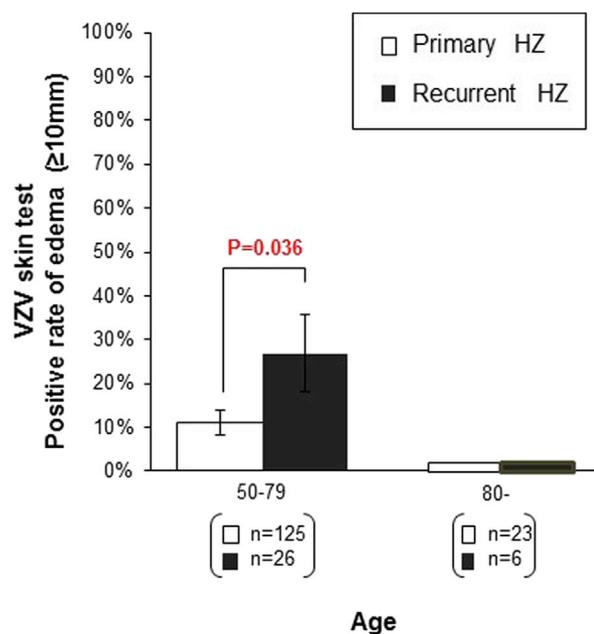
VZV-specific CMI may be stronger in patients with recurrent HZ because reactivation of primary VZV

infection boosts immunity against VZV. We previously reported that CMI for VZV was inversely associated with the severity of skin lesions and HZ-associated acute/subacute pain.<sup>12</sup> These findings suggest that the stronger VZV-specific CMI observed in patients with recurrent HZ in the current study may reduce the severity of skin lesions and acute pain in this group. We have also previously reported that patients with HZ with a strong VZV skin test response had a significantly lower risk of PHN than patients with a weak skin test response.<sup>13</sup> That report is consistent with our current finding that recurrent HZ is associated with a lower risk of PHN.

In patients aged 80 years and older with primary or recurrent HZ, there were no significant differences in the severity of skin lesions and acute pain, the incidence of PHN, and CMI for VZV. There are 2



**Fig 3.** Incidence of postherpetic neuralgia (PHN) between primary and recurrent herpes zoster (HZ) by logistic regression analysis in 2 age groups (50-79 vs  $\geq 80$  years). Bars indicate the mean incidence of PHN adjusted for sex (error bars, SEM).



**Fig 4.** Percentage of patients with edema ( $\geq 10$  mm) in the varicella-zoster virus (VZV) skin test among patients with primary and recurrent herpes zoster (HZ) in 2 age groups (50-79 vs  $\geq 80$  years). Bars indicate the mean positive rate of edema ( $\geq 10$  mm) adjusted for sex (error bars, SEM).

possible explanations for these findings. First, although we have no precise data about the interval period between primary and recurrent HZ in individual patients, it is possible that the patients with later onset of primary HZ might develop a

weaker booster response to VZV and thereby be susceptible to recurrent HZ despite a recent episode of primary HZ. Second, in patients with earlier onset of primary HZ, immunity to VZV might be expected to decrease with aging and recurrent HZ could occur after a long interval.

It has been reported that the risk of recurrent HZ ranges from 1% to 6%, with most studies showing that the annual incidence of recurrent HZ is nearly 1%.<sup>23</sup> We obtained a similar finding, with the annual incidence of recurrent HZ being 1.01%.

In this study, there was no significant difference in the incidence of recurrent HZ between men and women or between immunocompetent and immunocompromised patients. In contrast to our findings, previous studies conducted in clinics or hospitals have shown that the incidence of recurrent HZ and primary HZ are higher in women than in men.<sup>24</sup> This discrepancy is most likely a result of the differences in study design. We performed a community-based cohort study that included patients who do not usually seek medical attention unless specifically asked to do so. In addition, we found that recurrent HZ-associated pain tended to be less severe in men than in women, suggesting that men may be less likely to seek medical attention (data not shown). For the above 2 reasons, the incidence of HZ in men might be underreported by studies conducted in clinics or hospitals.

Because the risk of HZ increases as the population ages and the proportion of elderly persons in the population is continuously increasing in Japan, the incidence of recurrent and primary HZ are expected to rise substantially in the future. Our results showed that recurrent HZ could occur even if patients had stronger anti-VZV CMI. Therefore, identification of factors associated with recurrent HZ is required to allow the implementation of preventive measures.

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**SUPPLEMENTARY DATA**

The severity score for herpes zoster skin lesion was calculated as the sum of each score defined in

the table, on the basis of the distribution and properties of rash at the peak of disease activity.

Criteria for determining severity score of HZ skin lesions						
Score	Percentage of erythema in the lesional dermatome	Number of vesicles, pustules, erosions, or crusts	Fusion of vesicles	Ulcer formation	Number of lesional dermatomes	Generalized eruption
0	0	0	Absent	Absent	Single	Absent
1	< 20	< 10	Present	Present	More than one	Present
2	20-50	10-50				
3	≥ 50	≥ 50				