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Review

VZV-specific cell-mediated immunity, but not humoral immunity, correlates inversely with the incidence of herpes zoster and the severity of skin symptoms and zoster-associated pain: The SHEZ study

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ABSTRACT

Onset of herpes zoster (HZ) is thought to be related to a decline in cell-mediated immunity (CMI). However, until recently, there have been no large-scale prospective studies on the relationship between varicella-zoster virus (VZV)-specific CMI and the onset and severity of HZ. The Japanese researchers conducted a cohort study on VZV immunity in a population living on an island cluster, Shozu County in Japan, and examined the people who developed HZ during a follow-up period of three years to clarify the relationship between the onset and severity of HZ and immunity. In this study, they focused on the relationship between cell-mediated and humoral immunity and the onset and severity of HZ. CMI was measured by VZV skin test, and humoral immunity was assessed with serological tests for VZV-specific antibodies. A total of 12,522 people over the age of 50 were enrolled in this study, and 401 registrants were diagnosed as HZ. VZV-specific CMI assessed by VZV skin test showed a significant inverse relationship with the incidence of HZ and the severity of skin lesions and acute and subacute pain, and with the occurrence of postherpetic neuralgia. In contrast, VZV-specific antibody titer was not associated with the incidence and severity of HZ. These results suggest that VZV-specific CMI, but not humoral immunity, plays a key role in controlling the onset of HZ, the severity of skin lesions, and zoster-associated pain.

Contents

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1. Introduction

Varicella-zoster virus (VZV) causes varicella in childhood as an initial stage of infection [1,2]. After the establishment of initial infection, VZV is considered to exhibit latent infection of the sensory nerve ganglia of the host throughout its lifetime, and to be reactivated by immunocompromised status, aging, stress, and overwork, causing a herpes zoster (HZ) attack [3].

The decline of cell-mediated immunity (CMI) is thought to be related to the risk of HZ [4–6]. Hope-Simpson reported that HZ decreased when varicella is prevalent, based on a detailed epidemiological study of 192 HZ cases [4]. In addition, Thomas et al. reported that frequent contact with varicella children suppressed the onset of HZ in adults [7]. Toyama at al. also reported that, based on the results of an epidemiological study of 48,388 patients with HZ in Miyazaki prefecture in Japan, the pattern of onset of HZ has a mirror-image relationship with the pattern of varicella epidemics [8]. These findings suggest that contact with varicella patients enhances immunity to VZV and reduces the risk of developing HZ.

A high-dose live-attenuated VZV vaccine (Oka/Merck VZV vaccine: Zostavax) was shown to have a preventive effect, and was approved as a HZ vaccine in the USA in 2006 [9,10]. In Japan, the original Oka varicella vaccine (Biken, Japan) has been available for prevention of HZ among the elderly since 2016.

VZV-specific CMI has been considered to be important for suppressing the onset of HZ. However, until not long ago, the relationship between the degree of immune reduction and the onset of HZ and the role of humoral immunity in the prevention of HZ have not been well understood. In recent years, the Japanese researchers conducted a large-scale prospective cohort study in a population living on an island cluster, Shozu County in Japan (the SHEZ Study), to clarify the relationship between HZ and immunity [11–20].

2. Design of the SHEZ study

The study design was reported previously [11]. 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 skin test with VZV antigen [21] at registration to evaluate their level of VZV specific CMI. Participants were followed up for three years by telephone interview every four weeks. If they developed suspected HZ, the participants visited hospitals or clinics in Shozu County that were registered with the study, where their symptoms, severity of pain, and humoral immunity were evaluated. Humoral immunity was assessed by the serological tests for VZV-specific antibodies, i.e., the neutralization (N) test, immunoadherence hemagglutination (IAHA) test, and gpELISA test [21–26]. 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 participants who developed suspected 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 three dermatologists with expertise in HZ, and final diagnoses were 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.

2.1. VZV skin test

To evaluate the level of CMI, the researchers used skin test with the VZV antigen Biken (a commercially available reagent from the Research Foundation for Microbial Diseases of Osaka University, Japan). Detailed methods are described elsewhere [21]. Briefly, 100 ml of VZV skin test antigen was injected intradermally into the forearm, and erythematous changes and edema formation were judged 48 h after the injection. The greatest diameter was taken as the test result. The extent of edema was also assessed by palpation with the index finger.

2.2. Assessment of humoral immunity for VZV

Humoral immunity was assessed for the registrants who developed HZ at the initial medical visit. The serological tests for VZV-specific antibodies, i.e., neutralization (N) test, immunoadherence hemagglutination (IAHA) test, and gpELISA test, were performed as described previously [21–26].

2.3. Evaluation of HZ skin lesions

Initial evaluation of subjects with possible HZ was conducted by physicians in Shozu County using a standard survey form. The clinical diagnosis was confirmed by 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 other associated symptoms. 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 [14,15].

2.4. Evaluation of zoster-associated pain

The severity of pain was evaluated using a face scale from 0 (no pain) to 5 (pain disturbing sleep) [27] 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. 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. Patients with postherpetic neuralgia (PHN) were identified by conducting telephone interviews once every four weeks for each study participant who

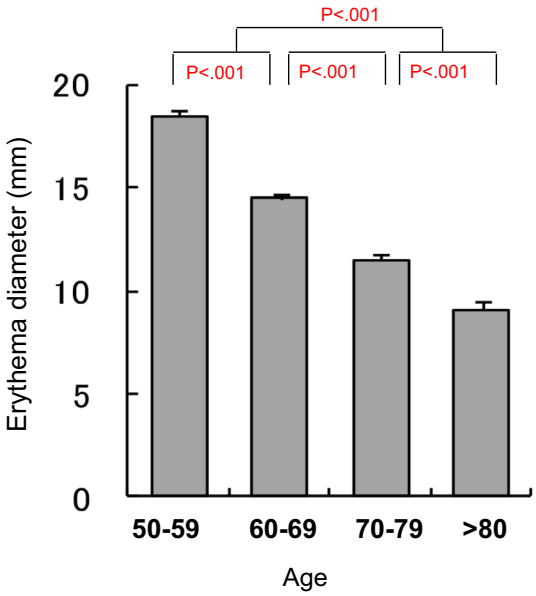

Fig. 1. Relationship of VZV skin-test reaction with sex and age.

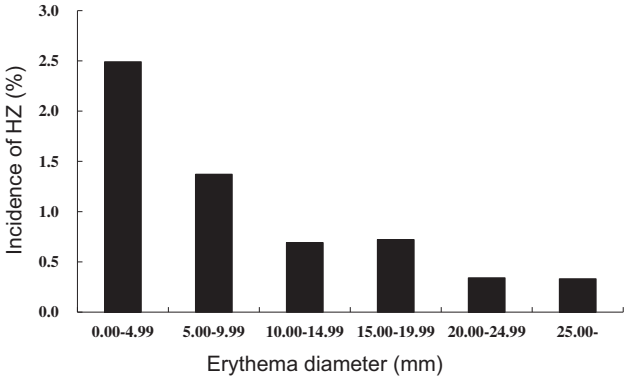

Fig. 2. Relationship of VZV skin-test reaction with incidence of HZ.

developed HZ. A diagnosis of PHN was made in patients with either (1) zoster-associated pain for at least three months after onset, or (2) recurrence of zoster-associated pain after three months or more.

3. Incidence of HZ and PHN [16]

Among the 12,522 subjects, 401 were definitively diagnosed as HZ from clinical symptoms and virological examination during the three-year study period, with an annual incidence of 1.07%. Among the 401 HZ patients, 79 (19.7%) developed PHN with persistent pain for three months or more.

4. Relationships of VZV skin-test reaction with sex and age [13]

There was no significant difference in greatest diameter of erythema caused by the skin test between men and women. The diameter of erythema significantly decreased with increasing age (Fig. 1). These results indicate that the increase of HZ incidence with age is associated with a decline in VZV-specific CMI, as suggested previously [5,6].

5. Relationship of VZV-specific cellular and humoral immunity with incidence of HZ [13,28]

The group with a stronger VZV skin-test reaction showed a lower incidence of HZ [13,28] (Fig. 2). For example, the hazard ratio of HZ for the group of erythema ≥10 mm vs. the group of erythema <10 mm was 0.27 (95% confidence interval: 0.19–0.37). In contrast, there was no significant correlation between VZV-specific antibody titer and HZ incidence. These results indicate that VZV-specific CMI plays an important role in preventing the development of HZ, whereas humoral immunity does not affect the onset of HZ.

6. Relationship of VZV-specific cellular and humoral immunity with severity of HZ skin lesions and zoster-associated acute and subacute pain [14]

Fig. 3 shows the relationship of VZV skin-test reaction with severity of skin lesions and acute and subacute zoster-associated pain. The diameters of erythema caused by the skin test showed a significant inverse relationship with both the severity score of skin lesions and the severity score of acute and subacute pain. The researchers also investigated the relationship of VZV-specific antibodies with the severity of skin lesions and acute and subacute zoster-associated pain. Assay for VZV-specific antibodies was also performed for registrants with HZ at their initial medical visit. In order to minimize the effect of VZV reactivation on the serum antibody titer, this analysis was restricted to those HZ patients who underwent an antibody test within three days of the onset of rash. The severity score of HZ skin lesions showed no relationship with the serum VZV-specific antibody titers determined by N test, IAHA test, or gpE-LISA test (Fig. 4**a–c**). The severity scores of acute and subacute zoster-associated pain also showed no relationships with the serum VZV-specific antibody titer (Fig. 4**d–f**). These results suggest that VZV-specific CMI, but not humoral immunity, plays a critical role in reducing the progression of HZ.

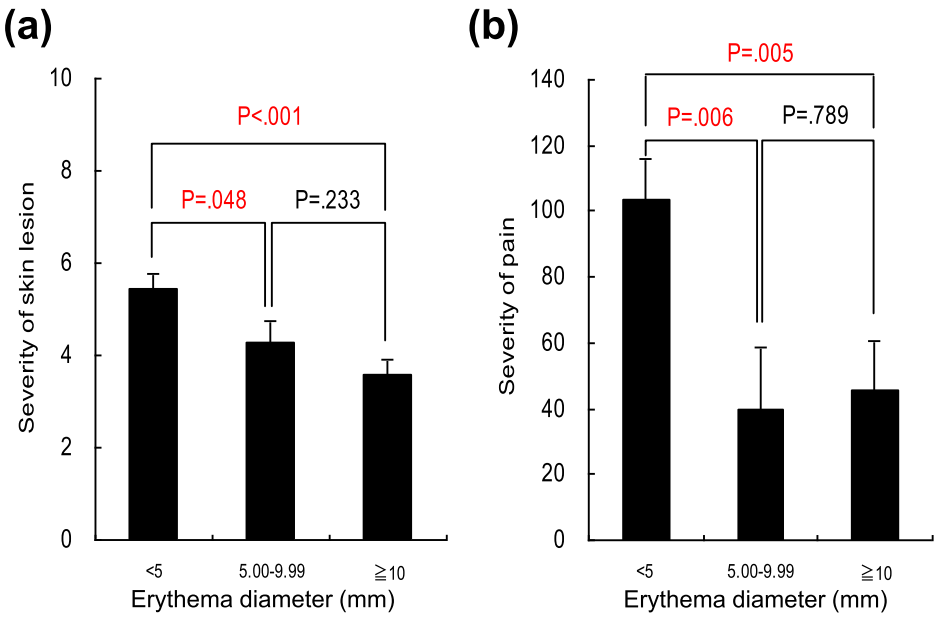

Fig. 3. Relationship of VZV skin-test reaction with severity of HZ skin lesions and acute and subacute zoster-associated pain. (a) Severity of skin lesions by diameter of erythema in the skin test. (b) Severity of pain by diameter of erythema in the skin test.

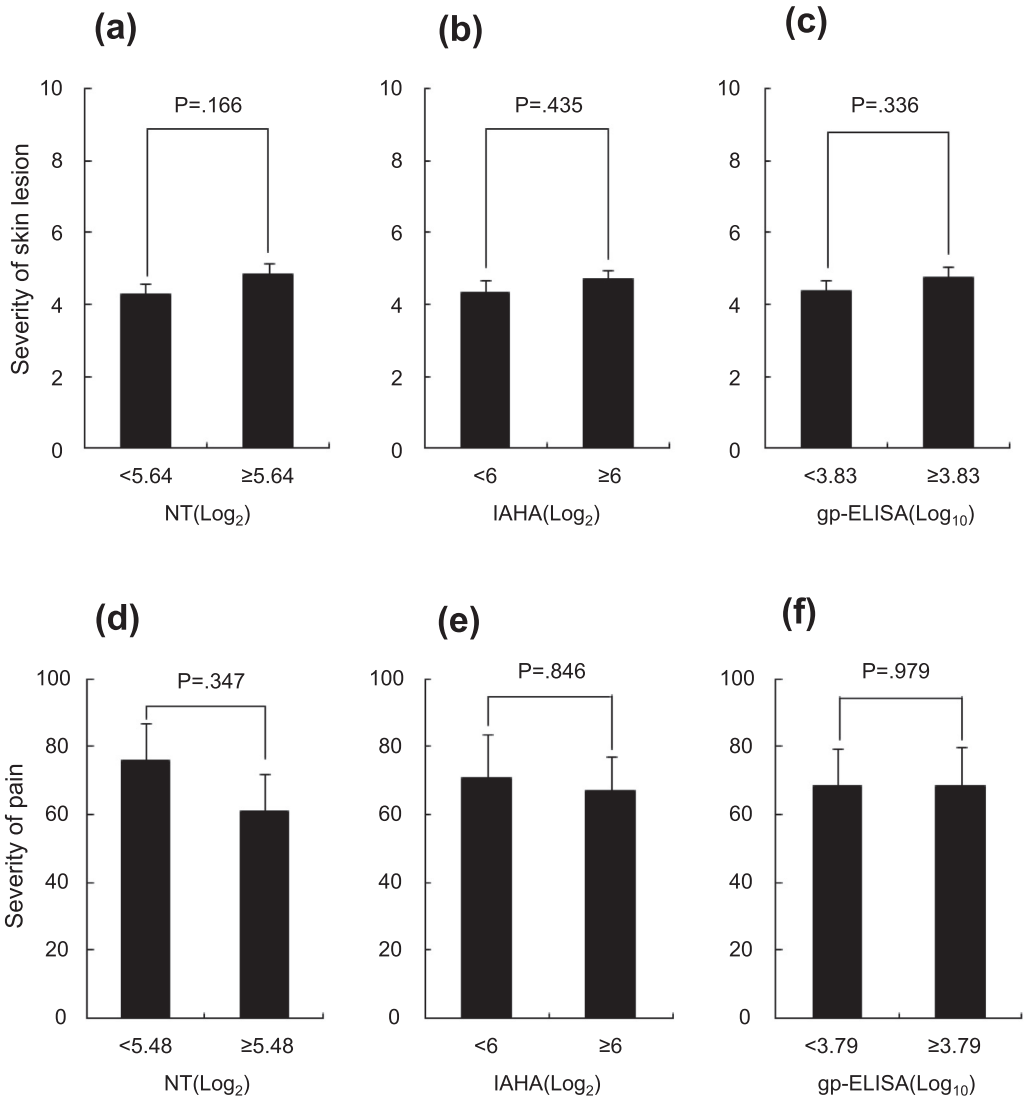

Fig. 4. Relationship of VZV-specific antibodies with severity of HZ skin lesions and acute and subacute zoster-associated pain. The patients were divided into two groups using the median of VZV-specific antibody titers, and the severity scores of HZ skin lesions and acute and subacute zoster-associated pain were compared between these two groups. (a) Severity of skin lesions by NT. (b) Severity of skin lesions by IAHA. (c) Severity of skin lesions by gp-ELISA. (d) Severity of pain by NT. (e) Severity of pain by IAHA. (f) Severity of pain by gp-ELISA.

7. Relationship of VZV-specific cellular and humoral immunity with PHN [15]

Regarding the relationship of the VZV skin-test reaction with PHN, HZ patients with a strong skin-test response (erythema ≥5 mm) showed a significantly lower risk of PHN than those with a weak skin-test response (erythema <5 mm) (Fig. 5**a**). HZ patients who had edema formation by the skin test showed a significantly lower incidence rate of PHN than those without edema formation (Fig. 5**b**). In contrast, the incidence rate of PHN showed no relationship to the serum VZV-specific antibody titers determined by N test, IAHA test, or gpELISA test. These results suggest that VZV-specific CMI, but not humoral immunity, plays a critical role in reducing the risk of PHN.

Weinberg et al. also demonstrated that a higher VZV-CMI response measured by in vitro immunological assay was associated with a lower occurrence of PHN [29]. Furthermore, Opstelten et al. reported that VZV-antibody titer had no predictive value for PHN development [30]. These two findings are supported by the results of the SHEZ Study.

8. Conclusions and future directions

The Japanese researchers carried out a large-scale prospective cohort study, and examined the participants who developed HZ during a follow-up period of three years, with a focus on the relationships of cell-mediated and humoral immunity to the onset of HZ and the severity of skin lesions and zoster-associated pain. They found that CMI to VZV assessed by the VZV skin test was inversely associated with the incidence of HZ, the severities of skin lesions and acute and subacute pain, and the occurrence of PHN. In contrast, VZV-specific humoral immunity was not associated with the incidence of HZ, the severity of skin lesions, or zoster-associated pain. These results suggest that VZV-specific CMI, but not humoral immunity, plays a critical role in limiting the reactivation and replication of latent VZV, and thus in reducing the risk of onset and progression of HZ and its complications.

Treatment outcomes of HZ have markedly improved since the introduction of anti-herpesvirus drugs, represented by acyclovir, in the 1980′s. However, prevention of HZ with vaccines remains important, since many patients still suffer over the long term due

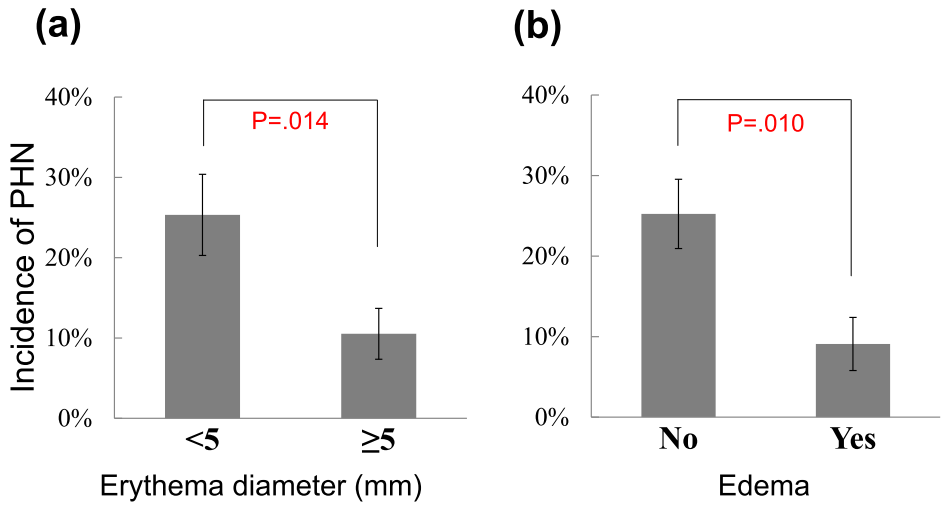

Fig. 5. Relationship of VZV skin-test reaction with incidence of PHN. (a) Patients with a strong response to the VZV skin test (erythema ≥5 mm) showed a significantly lower incidence of PHN. (b) Patients who had edema formation by skin test showed a significantly lower incidence of PHN.

to various complications and PHN. Our findings, indicating that VZV-specific CMI plays a key role in in preventing occurrence and limiting the severity of HZ and onset of PHN, may provide valuable information for the development of a more effective zoster vaccine and an immunization protocol to prevent HZ.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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