and Environmental Medicine, Graduate School of Medicine Osaka University, 2-2
Yamadaoka, Suita-shi, Osaka 565-0871, Japan
Phone: +81-6-6879-3911
Fax: +81-6-6879-3919
E-mail: iso@pbhel.med.osaka-u.ac.jp

Acknowledgements

The authors express their sincere appreciation to the cooperating medical organizations belonging to the Shozu County Medical Society: 11 of the 13 medical organizations in Shozu County consisting of 6 private clinics, 2 municipal clinics, 1 private hospital and 2 municipal hospitals. Dermatology department exists only at the 2 municipal hospitals, where dermatological services are provided by part-time dermatologists on 3 days a week, Shodoshima Federation of Self-Government Bodies, Tonosho Town Autonomous Liaison Council, Shodoshima Town Government and Tonosho Town Government, contributed greatly to the initiation of study.

Conduct of the study

The Shozu Herpes Zoster Study (SHEZ) is funded as "Epidemiological Research for the Development of Herpes Zoster Vaccine" (KHC1102) by a research grant from the Labour Sciences Research Grants at Research on Publicly Essential Drugs and Medical Devices of Health over 3 years starting in 2008. Research funds other than the grant-in-aid are supplied by the Research Foundation for Microbial Diseases of Osaka University.

The present members of the SHEZ and their affiliations are as follows: Prof. Koichi Yamanishi of the National Institute of Biomedical Innovation director-general presides over this study; Prof. Hideo Asada, Nara Medical University School of Medicine who is in charge of the evaluation of VZV skin tests, and the final diagnosis and evaluation for herpes zoster; Prof. Hiroyasu Iso, Osaka University School of Medicine which is in charge of the supervision of research planning and the analyses for the incidence of herpes zoster and postherpetic neuralgia and relationships of lifestyle and

sociopsychological factors with risk of herpes zoster; Prof. Yoshinobu Okuno, The Research Foundation for Microbial Diseases of Osaka University who is in charge of administration for the project, the organization of field work team, the measurements of neutralizing antibody, gp-ELISA, IAHA and the evaluation of the relationships of various immunological tests and herpes zoster; Prof. Yasuko Mori, The National Institute of Biomedical Innovation who is in charge of the measurements of ELISPOT and the evaluation of the correlation between ELISPOT and VZV skin test.

Introduction. Previous cross-sectional and cohort studies mostly in western countries have examined the incidence and risk factors for herpes zoster. However, the evidence from Asians has been limited and no cohort study has been conducted in Asian countries. We carried out a3-year cohort study in Shozu County, Kagawa Prefecture to clarify the incidence, predictive and immunological factors for herpes zoster among Japanese.

Methods. We recruit registrants and make them a follow-up for 3 years, doing telephone surveys once every 4 weeks. The registrants are classified into study A, B, and C by study contents. We conduct past history of herpes zoster and health questionnaires for study A registrants, Varicella-zoster virus (VZV) skin test for study B registrants, and blood tests for study C registrants as a basic survey. If the registrants develop herpes zoster, we conduct 1) evaluation of clinical symptoms, 2) measurement of cell-mediated immunity and humoral immunity using venous blood sampling, 3) photography of skin areas with rash, 4) virus identification tests by PCR and virus isolation from crust sampling, and 5) evaluation of postherpetic pain.

Results. We recruited successfully 12,522 registrants with 72.3% participation rate of the target population aged ≥50 years in the Shozu County between December 2009 and November 2010.

Conclusions. The present study will provide the evidence on the incidence and predictive and immunological factors for herpes zoster in a defined community-based population of Japanese.

Introduction

Varicella-zoster virus (VZV) causes varicella in childhood as an initial stage of its infection.[1,2] After the establishment of initial infection, VZV is considered to latently infect the sensory nerve ganglia of host throughout its lifetime and, to be reactivated by immunocompromisation, aging, stress, overworking, and decline in cell-mediated immunity, and to cause herpes zoster.[3]

Previous epidemiological studies on herpes zoster have shown the incidence rate,[4-7] age[4-10, 13-15] and gender[4, 6-12] difference, seasonality,[6-7, 9, 13, 16-17] family history,[21-22] underlying diseases,[12, 23-27] lifestyle factors[18-19] and sociopsychological factors.[6, 19-20]

In the United States, Oka/Merck VZV vaccine with at least 14 times higher potency than that of Varivax of Oka/Merck strain has been used. That vaccine was shown to have a preventive effect, was approved as a herpes zoster vaccine,[4] and is now recommended for individuals aged ≥60 years by the Advisory Committee for Immunization Practices (ACIP).[7]

In Japan, however, no epidemiological study on herpes zoster has been conducted and its epidemiology remains unclear. Therefore, no herpes zoster vaccine has been developed in this country.

We carry out a 3-year prospective cohort study in Shozu County, Kagawa Prefecture to clarify the incidence and predictive and immunological factors for herpes zoster. Herpes zoster is believed to occur when cell-mediated immunity declines,[28-29] but no data have been available what cell-mediated immunity level is critical for the clinical occurrence. Therefore, in this study, we clarify the relationship of the state of cell-mediated immunity evaluated by VZV skin test using Varicella antigen "Biken"[30-32] and quantified by

immunity measurements with risk of herpes zoster. If the skin test is proven useful as a predictor for herpes zoster, a high risk group can be identified. The skin test may also provide a useful index for the estimation of vaccine effectiveness.

Methods

Research community

Shozu County, Kagawa Prefecture is an administrative division, consisting mainly of Shodoshima Island (area: 153.30 km²) and Teshima Island (area: 14.49 km²) with a census population of 33,782, of which 32.8% were ≥aged 65 years on July 1, 2008. That research county was selected from the following four criteria: 1) a stable population, 2) the use of self-government bodies, by which information can be transmitted smoothly through the population, leading to a high registration rate, 3) good cooperation by clinics and hospitals in the islands, where most residents consult these medical organizations, facilitating the acquisition of information concerning the occurrence of herpes zoster in the cohort and 4) the establishment of field research team which collects biological samples (blood, crust, or bulla fluid) from those who have developed the disease, and transport rapidly the samples to the central laboratory.

Target population and registrants

The target population is residents of Shozu County with Japanese nationality aged ≥50 years on October 1, 2008. Although herpes zoster occurs in persons of all ages, its incidence rapidly increases after the age of 50 years.[10,15] Then, the target population was restricted to those aged ≥50 years.

The provisional registrant is a person who singed a registration form. The items of the registration form were address, telephone number, name, gender, date of birth, age, study category of the subject's choice, clinics or hospitals that the subject will probably consult if he/she develop herpes zoster, and time of the day convenient for telephone surveys. The documents necessary to complete registration were sent to 12,896 provisional registrants by confidential mail, and those who completed the procedure were formally registered. Eventually, there were 12,522 final registrants (registration rate: 72.3%).

Study period

The survey period is 3 years after registration between April, 2009 and November, 2012.

Study category

As shown in Table 1. There are three studies A, B, and C. In study A, we conducted a questionnaire and telephone survey and, if the subject develops herpes zoster during the study period, surveys at the onset and the recovery stage, as a basic survey. Study B was the VZV skin test at registration to examine the state of cell-mediated immunity during a healthy period in addition to the basic survey. Study C was to examine cell-mediated (ELISPOT) and humoral immunity (neutralizing antibody, gp-ELISA and IAHA) using serum at registration and after 1, 2, and 3 years for subjects selected from those who have undergone study B.

The registrants chose one of the three studies under the restriction in the number of entries, i.e., 5,000 to 7,500 for study B and 200 to 300 for study C. The participants in study C were selected by drawing lots, because the registrants who wished the enrollment

exceeded the target numbers. As a result, 5,685 and 365 of the 12,522 registrants were enrolled in studies B and C, respectively.

Study hypotheses

We attempted to verify the following major hypotheses in study A (Table 2); 1) the annual age-adjusted incidence of herpes zoster is approximately 10 per 1,000 persons aged ≥50 years,[4] 2) the incidence of herpes zoster and postherpetic neuralgia increases with age,[4-5] 3) there is no sex difference in the incidence of herpes zoster and postherpetic neuralgia,[4, 8, 10] 4) the incidence of herpes zoster is frequent mostly from July to October which is off season of chicken pox,[9, 13-14] but, there is no seasonality for postherpetic neuralgia, 5) underlying diseases, stress, sleep deprivation, inadequate intake of fruits and vegetables, smoking, drinking, depression, family history of herpes zoster increase risks of herpes zoster and postherpetic neuralgia,[12, 18-19, 22-27] 6) perceived good health, exercise, optimism, positive well-being and social support are associated with enhanced reaction in VZV test and decrease risks of herpes zoster and postherpetic neuralgia,[19, 20] and 7) the severer degree of pain at onset of herpes zoster, the higher risk for postherpetic neuralgia. The hypotheses in study B are 1) the state of cell-mediated immunity against herpes zoster can be evaluated by VZV skin test,[30-32] and 2) the higher degree of VZV skin test, the lower the risk and severity of herpes zoster and postherpetic neuralgia.[29] The hypotheses in study C are 1) the cell-mediated and humoral immunity levels decline with age,[32] and 2) without boosting effect by exposure to varicella-zoster virus, for example an epidemic of varicella, the cell-mediated and humoral immunity levels gradually decline.[16]

Interview for the past history

The interview was conducted to inquire a past history of herpes zoster at registration by research physicians. The question items are whether they have contracted herpes zoster before, time of its occurrence, and whether they saw a doctor. The responses were obtained from all 12,522 final registrants (100%).

For studies B and C, to increase the reliability of the past history, research physicians asked the symptoms and drugs administered, and judged whether the past event in question was herpes zoster.

Self-administered health questionnaires

The self-administered questionnaire survey was carried out to evaluate factors including diet, stress and overwork at registration, and, if there was inadequacy of entries, secretariat members checked them by asking the subjects.

The question items are self-rated health, smoking, exercise, walking time, sleep, degree of satisfaction with sleep, stress, diet (frequencies of fruits, vegetables, fish, meat, eggs, miso soup, soybeans, and milk intakes), drinking, personality, frequency of laughing, purpose of life, opportunities of conversation, spiritual support, life events, hobbies and interests, hopes, underlying diseases, familial history, height, and body weight. The valid answers were obtained from 12,360 (98.7%) of the 12,522 final registrants.

Telephone surveys

Telephone surveys are commissioned to a contract organization (Bellsystem24 Inc.), which performed them according to an established talk script at frequency of once every

4 weeks during the study. All registrants are asked whether they had developed symptoms suggestive of herpes zoster. One registrant of each family answered the surveys, representing all registrants in the family.

The questions concerned the presence or absence of rash, pain, history of contact with a varicella patient, and admission to clinic or hospital. If a registrant reported both rash and pain, this information is automatically transmitted to the secretariat, and the survey on the onset is initiated.

VZV skin test

We used Varicella antigen "Biken" (The Research Foundation for Microbial Diseases of Osaka University) to evaluate the sensitivity or the state of cell-mediated immunity. The test is performed by the intradermal inoculation of varicella antigen "Biken" at 0.1 mL/injection and the examination of the state at inoculation site after 48 hours. VZV skin test was performed at registration in 5,685 registrants enrolled in Study B.

Blood tests

Blood tests were performed in the registrants enrolled in Study C. Cell-mediated (ELISPOT) and humoral (neutralizing antibody, gp-ELISA and IAHA) immunity was examined at the baseline and after 1, 2, and 3 years.

Surveys at the onset and recovery

A survey at the onset is initiated if a cooperating physician makes the diagnosis of "herpes zoster" or "possible herpes zoster."

The survey at the onset consists of five items: 1) evaluation of clinical symptoms, 2) measurement of cell-mediated (ELISPOT) and humoral (neutralizing antibody, gp-ELISA and IAHA) immunity using venous blood sampling, 3) virus identification tests by PCR and virus isolation from crust sampling, 4) evaluation of pain, and 5) photography of the skin areas with rash.

The survey during recovery consists of two items: 1) evaluation of sequelae and 2) measurement of cell-mediated (ELISPOT) and humoral (neutralizing antibody, gp-ELISA and IAHA) immunity using venous blood sampling.

Clinical symptoms are evaluated the severity of symptoms and of treatment by a physician using a survey form. The evaluation items are the presence or absence of underlying diseases, the use of an immunosuppressant or antineoplastic agent, date of rash appearance, distribution of rash, properties of rash (the presence or absence of erythema; numbers of vesicles, pustules, and erosions; and the presence or absence of ulceration, fusion, and bloody vesicles), date of pain appearance, other specific symptoms (fever, headache, generalized herpes zoster, multidermatomal herpes zoster, eye complications, motor paralysis, Ramsay Hunt syndrome and others), and treatment.

The evaluation of onset and postherpetic pain is carried out by secretariat members using a modifed the Zoster Brief Pain Inventory survey form [33]. The question items were the presence or absence of stress and pain, distribution of pain, severity of pain according to a face scale from 0 (no pain) to 5 (sleep disturbing pain), changes in the tactile sensation in painful areas, treatment for pain or medication, and the Quality of Life (activities of daily living, psychology, work and housework, social events, sleep and hobbies).

The questionnaires are planned to conduct at days 0, 1, 2, 3, 4, 5, 6, 13, 20, 27, 34, 41, 48, 55, 85, 115, 145, 175 after the initial examination. The questionnaires are ended with the disappearance of pain but are continued for at least 7 days. Also, the presence or absence of mental stress is evaluated at the initial examination alone, and the treatment or medication for pain is evaluated at the initial, weekly and monthly examinations.

The survey during recovery is carried out by a physician using a survey form concerning the presence or absence of sequelae (postherpetic neuralgia, motor paralysis, scars and others).

Definite diagnosis of herpes zoster

All subjects with initial clinical diagnosis of "herpes zoster" or "possible herpes zoster" were examined by PCR analysis for VZV, HSV and beta-globin DNA in fluid from the vesicles, and were studied by serological analysis for anti-VZV antibodies using paired serum, and had clinical photographs taken. The final diagnosis was determined by comprehensive evaluation of clinical symptoms, results of PCR and serological tests, under the responsibility of clinical evaluation committee, consisting of three dermatologists with expertise in herpes zoster, Nara Medical University School of Medicine.

If the PCR assay revealed VZV DNA, the final diagnosis was herpes zoster; if the assay was positive for beta-globin or HSV DNA and negative for VZV DNA, the final diagnosis was not herpes zoster. If the specimen obtained for PCR assay was inadequate (i.e., was negative for both viral and beta-globin DNA) or was missing, the final diagnosis was determined on the basis of serological test and clinical symptoms by the

clinical evaluation committee. Registrants with a final diagnosis of herpes zoster are regarded as definitively-diagnosed patients.

Dropouts

Registrants are regarded as having dropped out when the continuation of survey is judged to be impossible due to their death, impaired cognitive function, move-out of surveyed areas, when registrants have announced withdrawal from the study, or when no response has been obtained on 3 or more telephone survey. Death of registrants is confirmed by cooperation of the municipal administration according to their names and dates of birth.

Sample size calculation

Of the target population of 19,138 (as of June 1, 2007), a total of 12,000 or more (≥62.7%) are aimed to be registered for study A (Table 1). The incidence of herpes zoster is calculated separately for each gender and age category (50-59, 60-69 and ≥70). In previous studies in Japan and abroad, the annual incidence of herpes zoster has been reported to be 0.50-0.60% for persons aged 50-59 years, 0.60-1.0% for those aged 60-69 years, and 0.90% for those aged ≥70 years without gender difference.[4, 5, 9]

When the expected numbers of patients during the 3-year study period are calculated by multiplying the median value of incidence in each age category (0.55% for persons aged 50-59 years, 0.80% for those aged 60-69 years, and 0.90% for persons aged ≥70 years) by the census populations of the respective age category in Shozu County (Table 1), 48 men and 47 women aged 50-59 years, 53 men and 59 women aged 60-69 years, and 90 men and 146 women aged ≥70 years are expected to develop herpes zoster.

Since approximately 30 or more patients to develop herpes zoster during the 3-year survey period by gender and age category are necessary to calculate gender and age-specific incidence with sufficient reliability, the participation of 63% of total population of Shozu County is necessary. The population of Shozu County aged ≥50 years is 19,138, and thus approximately 12,000 is the target number of registrants. Under these conditions, a difference in the incidence during the 3-year survey period between men aged 50-59 years (n=2,891) and those aged ≥70 years (n=3,323) can be detected at a significance level of 5% and a statistical power of 80%.

To examine the relationship between VZV skin test and risk of herpes zoster for study B, the skin test result is classified into tertiles (33 percentiles), and the 3-year incidence in the high-reaction group (upper 33 percentiles) is assumed to be 1.2% (annual incidence: 0.4%). When the risk of herpes zoster in 1,600 (to maximum 2,500) registrants of the high-reaction group relative to that in 1,600 (to maximum 2,500) registrants of the low-reaction group (lower 33 percentiles) is calculated, the association between the VZV skin test result and risk of herpes zoster can be detected if the relative risk is 2.1 or greater (under 1,600 registrants for each tertile) and 1.9 or greater (under 2,500 registrants for each tertile) at a significance level of 5%, analytical power of 80%, and follow-up rate of 90%. Thus, we aimed to obtain 5,000 to 7,500 participants for study B (Table 1).

For evaluating the duration of cell-mediated and humoral immunity in study C, the state of immunity is classified into tertiles (33 percentiles), and analysis is performed separately for genders. To secure 30 or more registrants in each tertile group for each gender, the target number of enrollment is 200 to 300.

Ethical issues

Informed consent for the study was obtained from study B and C registrants, and for study A registrants, the return of questionnaires was regard as consent to participate in the study.

The present study was approved by the Ethics Committee of the Research Foundation for Microbial Diseases of Osaka University, Osaka University Graduate School of Medicine, National Institute of Biomedical Innovation, and Nara Medical University School of Medicine.

Results

The target census population are 19,058 individuals (8,424 men and 10,634 women in total), consisting of 5,362 (2,710 and 2,652) aged 50-59 years, 4,918 (2,383 and 2,535) aged 60-69 years, 4,897 (2,064 and 2,833) aged 70-79 years, and 3,881 (1,267 and 2,614) aged ≥80 years.

Table 3 shows the number of registrants and their age distribution, and past history of herpes zoster. We successfully recruited 12,522 registrants (72.3% of all residents) for study A, 5,685 registrants for study B and 365 registrants for study C. Compared with the census population, the registrants for study A showed a similar mean and distribution of age, but those for study B had a slightly lower mean ($P<0.001$), higher percentages of ages 50-59 years and 60-69 years, and lower percentage of ages ≥80 years (P for distribution difference <0.001). In study A, the prevalence of the self-reported past history of herpes zoster were 12.7% for men and 20.1% for women, indicating the higher

past history in women than in men (P<0.001). When stratified by age group, a similar gender difference was found in each age group (Table 4).

Discussion

We recruited successfully a total of 12,522 registrants with 72.3% participation rate of the target population aged ≥50 years in the Shozu County. To ensure a high follow-up and complete as certainement of the occurrences of herpes zoster, a systematic telephone survey is undertaken. The residents are informed of the study by notices put up on bulletin boards and PR brochures every 3 months to enhance the residents' interest, and knowledge about herpes zoster, and to stimulate their early consultation to medical facilities. The early consultation is expected to contribute to the early administration of antiviral agents, leading to reduction of severe herpes zoster and postherpetic neuralgia.

In addition, the increased knowledge about herpes zoster in the residents of the survey community is considered to promote residents with mild herpes zoster, to see a physician in local hospital or clinic, which also contribute to the determination of the accurate incidence.

The occurrence of herpes zoster has been reported to be affected by epidemics of varicella.[13, 16] Since epidemics of varicella have been related to the status of vaccination, the varicella epidemics and vaccination status are monitored in the survey community through Infectious Diseases Weekly Report Kagawa, annual sales report of BIKEN's varicella vaccine, and population census.

In Shozu County, the numbers of the varicella symptoms observed varied between 2001 and 2010 in which the average numbers reported from two pediatrics sentinel

clinics in the area during the above 10 years was 113.5 people (minimum 22 up to maximum 266) , with an epidemic of ≥150 people cases in 2002, 2004 and 2010 according to Infectious Diseases Weekly Report Kagawa. The proportion of vaccination against varicella was 51.4% (amount of vaccine sold in 2008, divided by the number of childbirths in 2007). This proportion was 9.8% higher than that in Japan national average according to annual sales report of BIKEN's varicella vaccine and population census. Therefore, it is necessary to investigate the vaccination status and outbreaks continuously, and to verify its relationship with the incidence of herpes zoster.

The present study will provide the evidence on the incidence and predictive and immunological factors for herpes zoster in a defined community-based population Japanese.

References

1. Grose C. Variation on a theme by Fenner: the pathogenesis of chickenpox. Pediatrics. 1981; 68: 735-7.
2. Ku CC, Besser J, Abendroth A, Grose C, Arvin AM. Varicella-Zoster virus pathogenesis and immunobiology: new concepts emerging from investigations with the SCIDhu mouse model. J Virol. 2005; 79: 2651-8.
3. Mims CA, White DO. Viral pathogenesis and immunology. Blackwell Scientific Publications 1984.
4. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005; 352: 2271-84.
5. Yawn BP, Saddier S, Wollan PC, St Sauver JL, Kurland M, Sy LS. A population-based study of the incidence and complications of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007; 82: 1341-9.
6. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis. 2004; 4: 26-33.
7. Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2008; 57: 1-30.
8. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med. 1995; 155: 1605-9.

1 9. Toyama N, Shiraki K, Society of the Miyazaki Prefecture Dermatologists.
2 Epidemiology of herpes zoster and its relationship to varicella in Japan: A 10-year
3 survey of 48,388 herpes zoster cases in Miyazaki Prefecture. J Med Virol. 2009; 81:
4 2053-8.
5 10. Hope-Simpson RE. Postherpetic neuralgia. J R Coll Gen Pract. 1975; 25: 571-5.
6 11. Opstelten W, Van Essen GA, Schellevis F, Verheij TJ, Moons KG. Gender as an
7 independent risk factor for herpes zoster: a population-based prospective study. Ann
8 Epidemiol. 2006; 16: 692-5.
9 12. Soyuncu S, Berk Y, Eken C, Gulen B, Oktay C. Herpes zoster as a useful clinical
10 marker of underlying cell-mediated immune disorders. Ann Acad Med Singapore.
11 2009; 38: 136-8.
12 13. Yih WK, Brooks DR, Lett SM, Jumaan AO, Zhang Z, Clements KM, et al. The
13 incidence of varicella and herpes zoster in Massachusetts as measured by the
14 Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing
15 varicella vaccine coverage, 1998-2003. BMC Public Health. 2005; 5:1-9.
16 14. Lin YH, Huang LM, Chang IS, Tsai FY, Lu CY, Shao PL, et al, Varicella-Zoster
17 Working Group, Advisory Committee on Immunization Practices, Taiwan. Disease
18 burden and epidemiology of herpes zoster in pre-vaccine Taiwan. Vaccine. 2010; 28:
19 1217-20.
20 15. Chapman RS, Cross KW, Fleming DM. The incidence of shingles and its
21 implications for vaccination policy. Vaccine. 2003; 21: 2541-7.

16. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. Lancet. 2002; 360: 678-82.
17. Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, et al. Epidemiology of varicella zoster virus in Canada and the United Kingdom. Epidemiol Infect. 2001; 127: 305-14.
18. Thomas SL, Wheeler JG, Hall AJ. Micronutrient intake and the risk of herpes zoster: a case-control study. Int J Epidemiol. 2006; 35: 307-14.
19. Schmader K, George LK, Burchett BM, Pieper CF. Racial and psychosocial risk factors for herpes zoster in the elderly. J Infect Dis. 1998; 178 Suppl 1: S67-70.
20. Irwin M, Costlow C, Williams H, Artin KH, Chan CY, Stinson DL, et al. Cellular immunity to varicella-zoster virus in patients with major depression. J Infect Dis. 1998; 178 Suppl 1: S104-8.
21. Gatti A, Pica F, Boccia MT, De Antoni F, Sabato AF, Volpi A. No evidence of family history as a risk factor for herpes zoster in patients with post-herpetic neuralgia. J Med Virol. 2010; 82: 1007-11.
22. Hicks LD, Cook-Norris RH, Mendoza N, Madkan V, Arora A, Tyring SK. Family history as a risk factor for herpes zoster: a case-control study. Arch Dermatol. 2008; 144: 603-8.
23. Heymann AD, Chodick G, Karpati T, Kamer L, Kremer E, Green MS, et al. Diabetes as a risk factor for herpes zoster infection: results of a population-based study in Israel. Infection. 2008; 36: 226-30.