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ORIGINAL ARTICLE

Herpes zoster could be an early manifestation of undiagnosed human immunodeficiency virus infection

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KEYWORDS
herpes zoster;
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Background/Purpose: No formal epidemiological research based on systematic analysis has focused on the relationship between herpes zoster and immunodeficiency virus (HIV) infection in Taiwan. Our aim was to explore whether herpes zoster is an early manifestation of undiagnosed human HIV infection in Taiwan.
Methods: This was a retrospective cohort study using the database of the Taiwan National Health Insurance Program. A total of 35,892 individuals aged ≤ 84 years with newly diagnosed herpes zoster from 1998 to 2010 were assigned to the herpes zoster group, whereas 143,568 sex-matched and age-matched, randomly selected individuals without herpes zoster served as the non-herpes zoster group. The incidence of HIV diagnosis at the end of 2011 was estimated in both groups. The multivariable Cox proportional hazards regression model was used to estimate the hazard ratio and 95% confidence interval (CI) for risk of HIV diagnosis associated with herpes zoster and other comorbidities including drug dependence and venereal diseases.
Results: The overall incidence of HIV diagnosis was 4.19-fold greater in the herpes zoster group than that in the non-herpes zoster group (3.33 per 10,000 person-years vs. 0.80 per 10,000 person-years, 95% CI 4.04–4.35). The multivariable Cox proportional hazards regression analysis revealed that the adjusted hazard ratio of HIV diagnosis was 4.37 (95% CI 3.10–6.15) for individuals with herpes zoster and without comorbidities, as compared with individuals without herpes zoster and without comorbidities.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: Herpes zoster is associated with HIV diagnosis. Patients who have risk behaviors of HIV infection should receive regular surveillance for undiagnosed HIV infection when they present with herpes zoster.

Introduction

Herpes zoster, commonly known as shingles, is caused by reactivation of latent varicella-zoster virus in the cranial-nerve or dorsal-root ganglia.[1,2] It is clinically characterized by painful grouped vesicles on a erythematous rash along the dermatome area, and it can result in chronic severe pain (postherpetic neuralgia), particularly in older people.[1–3] To date, multiple risk factors of herpes zoster have been well established, including immunosuppressive conditions, cancers, and chronic medical conditions.[3–6] In addition, a growing body of evidence reveals that the prevalence of human immunodeficiency virus (HIV) infection is considerably high among persons with high-risk behaviors presenting with herpes zoster.[7–9] Some studies have also revealed that herpes zoster could be an early manifestation of undiagnosed HIV infection because of an early defect in cell-mediated immunity.[9–12] In Taiwan, the first HIV patient was found in 1984, and at the end of 2013, the total number of HIV patients had reached 26,475.[13] To date, no formal epidemiological research based on systematic analysis has focused on the relationship between herpes zoster and HIV infection in Taiwan. If herpes zoster is really an early manifestation of undiagnosed HIV infection, patients with high-risk behaviors of HIV infection should undergo testing for undiagnosed HIV infection when they present with herpes zoster. Therefore, we conducted a population-based cohort study using the database of the Taiwan National Health Insurance Program to explore this issue.

Methods

Design and study population

This was a retrospective cohort study using the database of the Taiwan National Health Insurance Program. The program, which was implemented in March 1995, covers almost 99% of 23 million people living in Taiwan.[14] The details of the program have been well written in previous high-quality studies.[15–17] The study was approved by the Institutional Review Board of China Medical University and Hospital in Taichung, Taiwan (CMUH-104-REC2-115).

Study participants, comorbidities, and main outcome measurement

We identified individuals aged $\leq$ 84 years with newly diagnosed herpes zoster as the herpes zoster group from 1998 to 2010, based on the International Classification of Diseases, 9th Revision (ICD-9 code 053). The date of diagnosing herpes zoster was defined as the index date. Four folds of comparison individuals without herpes zoster were randomly selected from the same database to serve as the non-herpes zoster group. The non-herpes zoster participants were matched with the herpes zoster participants by sex, age (every 5-year span), comorbidities, and the index year of diagnosing herpes zoster. We excluded individuals with HIV diagnosis (ICD-9 codes 795.71, V08, 042, and 079.53) at the baseline in both groups. The following potential risk factors for HIV infection were used: drug dependence (ICD-9 code 304) and venereal diseases (ICD-9 codes 090—099). All study participants were followed until they were diagnosed with HIV infection or until the end of 2011.

Statistical analysis

The distributions of sex, age, and comorbidities were compared between the herpes zoster group and the non-herpes zoster group using the Chi-square test for categorized variables and *t* test for continuous variables. The incidence of HIV diagnosis was estimated as the number of HIV diagnosis event identified during the follow-up period, divided by the total follow-up person-years for each group. The multivariable Cox proportional hazards regression model was used to estimate the hazard ratio and 95% confidence interval (CI) for risk of HIV diagnosis associated with herpes zoster and other comorbidities. The proportional hazard model assumption was also examined using a test of scaled Schoenfeld residuals. In the model evaluating the risk of HIV diagnosis throughout overall follow-up period, results of the test revealed a significant relationship between Schoenfeld residuals for herpes zoster and follow-up period, suggesting that the proportionality assumption was violated ($p = 0.002$). In the subsequent analyses, we stratified the follow-up period to deal with the violation of proportional hazard assumption. The statistical significance level was set at two-sided $p < 0.05$. All analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of the study population

Table 1 shows the distributions of sex, age, and comorbidities between the herpes zoster group and the non-herpes zoster group. There were 35,892 individuals in the herpes zoster group and 143,568 individuals in the non-herpes zoster group, with similar distributions of sex and age. The mean ages (standard deviation) of the study participants were 51.6 $\pm$ 19.1 years for the herpes zoster group and 51.2 $\pm$ 19.2 years for the non-herpes zoster group. The