Diabetes as a Risk Factor for Herpes Zoster Infection: Results of a Population-Based Study in Israel

A.D. Heymann, G. Chodick, T. Karpati, L. Kamer, E. Kremer, M.S. Green, E. Kokia, V. Shalev

Abstract

Background: Studies showed that diabetes mellitus (DM) is often accompanied by impaired cell-mediated immunity, which potentially may increase the risk for infectious diseases, including herpes zoster (HZ). However, data on the relation between DM and HZ are scarce. This case-control study explored the association between DM and HZ.

Patients and Methods: This study was nested within a cohort of all members of a large health maintenance organization (HMO) in Israel. Cases totaled 22,294 members who were diagnosed with HZ between 2002 and 2006. Controls (n = 88,895) were randomly selected from the remaining HMO population using frequency-matched age, sex, and duration of follow-up. Personal data on history of DM, lymphoma, leukemia, or AIDS, were obtained from computerized medical records.

Results: Adjusted analyses showed that the risk of HZ was associated with history of leukemia, lymphoma, use of steroids or antineoplastic medications, and AIDS, particularly among patients below 45 years of age. In a multivariate analysis, DM was associated with an increased risk of HZ (OR = 1.53; 95% CI: 1.44–1.62).

Conclusions: The data suggest that individuals with DM are at increased risk of HZ. Well-designed cohort studies may help to clarify the nature of this association.

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Herpes-zoster (HZ) or shingles is a fairly common infectious disease, which results from the reactivation of the varicella-zoster virus (VZV) acquired during primary varicella-zoster infection. Prior to the introduction of the varicella vaccine, the prevalence of naturally occurring infection was greater than 90% of the populations in the Western world [1]. After an acute VZV infection, latent infection is established in the sensible ganglia. Older individuals, patients with neoplastic diseases (especially lymphoproliferative cancers), immunocompromised patients, and persons who are seropositive for human immunodeficiency virus (HIV) are at increased risk of HZ due to their altered cell-mediated immunity [2].

Diabetes mellitus (DM) is often accompanied by impaired cell-mediated immunity and previous studies have shown the DM patients have infections more often than DM-free individuals [3]. The loss of cell-mediated immunity probably correlates with the duration of DM and impaired glycemic control [4]. Therefore, DM patients, and particularly patients with long-standing DM and poor glycemic control, are expected to have an increased risk of HZ. Nonetheless, a few early studies that have attempted to investigate the association between DM and HZ resulted in mixed conclusions [5, 6]. The aims of this study were to investigate the association between DM and the degree of glycemic control and the risk of HZ.

Patients and Methods

Data Source

For the current nested case-control study, we analyzed the databases of Maccabi Healthcare Services (MHS), the second largest health maintenance organization (HMO) in Israel, with a membership of 1.7 million people nationwide (24% of the general population) of whom 560,000 are under 18 years of age (25% of the general population in this age category). More than 90% of all MHS members are Jewish. The core of MHS operation is based on its 2,700 independent or salaried physicians and over 120 nation-wide community-clinics. According to Israeli National Health Insurance (NHI) act, MHS is obliged to insure every citizen who wishes to become a member, irrespective of age, sex, physical condition, or any other criterion. Under the NHI Act, round the clock accessibility to health services was

A.D. Heymann, G. Chodick (corresponding author), T. Karpati, L. Kamer, E. Kremer, E. Kokia, V. Shalev

Medical Division, Maccabi Healthcare Services, 27 HaMered St, Tel Aviv, 68125, Israel; Phone: (+972/3) 795 4450, e-mail: Hodik_g@mac.org.il

A.D. Heymann, G. Chodick, M.S. Green

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

A.D. Heymann and G. Chodick share equal contribution.

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clearly defined [7]. Thus, even in remote areas, MHS provides comprehensive primary care. The co-payment for physician visit is very low (limited to approximately US $ 5 a year for visits to primary-care physicians and US $ 20 a year for visits to specialized physicians). Each member has a unique identity number and medical charting is done exclusively in a computerized medical record. Specific data elements such as diagnoses, administrative data, laboratory results, and medication purchases are all recorded on the MHS’ central computerized databases. We used MHS database to identify all MHS members who were diagnosed with HZ and to obtain information on personal history of chronic diseases on all HZ cases and their controls. The study had no external funding source and its protocol was approved by the institutional review board of MHS.

Case Identification
All MHS members were followed from January 1st, 2002 until the diagnosis of first HZ outbreak, death, leaving MHS, or October 31st 2006, whichever occurred earlier. We identified HZ cases by an automated search for International Classification of Diseases, 9th revision code of HZ (ICD 9 code, 053) from primary-care physician consultation records and data on admissions from all general hospitals in Israel. The search was performed for all MHS members using an encrypted individual identification number.

During the study period, we identified 22,250 patients who were diagnosed with HZ either by family physicians (40%), dermatologists (36%), pediatricians (10%), or other physicians (14%) in community clinics or hospitals. To further evaluate the quality of the case identification, we examined the medical records of 87 randomly selected HZ patients. In 73 cases there was a definitive supporting clinical evidence of HZ, reflecting a minimal positive predictive value of 84% (95% CI: 78%–93%).

Control Population
Controls (n = 88,895) were selected using group matching according to sex, age (±1 year) and duration of follow-up, in a ratio of 1:4. Eligible controls were MHS members, who had no diagnosis of HZ or indication of use of Acyclovir, Valaciclovir, or Famciclovir throughout the entire follow-up period.

Collected Data
The following data were obtained for all study participants: age, sex, place of residence (categorized into northern, central and southern parts of Israel), personal history of lymphoma or leukemia, DM, or acquired immune deficiency syndrome (AIDS). For DM patients, the severity of the disease was measured by the median of hemoglobin A1c (HbA1c) levels during the year prior to the end of follow-up, duration of DM (categorized into <3 years and ≥3 years), and use of insulin for at least three years. We collected data also on dispensed prescriptions of antineoplastic and oral steroids in the year prior to the end of follow-up.

To investigate the relationship between DM and severe postherpetic neuralgia, the most common complication of HZ, we compared the proportion of patients with dispensed prescriptions of strong opioid drugs (e.g., Tramadol Hcl and Oxycodeone) within a year from HZ diagnosis among DM and DM-free subjects.

Statistical Analysis
For the nested case–control analysis, the odds ratios (OR) and 95% confidence intervals (CI) were calculated by unconditional logistic regression using SPSS version 14 (SPSS Inc., Chicago IL, USA). All the analyses were conducted after stratification by age (<45 years, 45–64 years, and 65 and above). Potential confounding between DM and HZ was investigated in multivariate models which included sex, place of residence, intake of antineoplastic or oral steroids, and personal history of leukemia, lymphoma, or AIDS.

The age-specific proportion of patients with dispensed prescriptions of opioids among DM and DM-free individuals were compared using chi-square test. The average number of dispensed prescriptions was compared using the nonparametric Mann-Whitney test.

Results
Incidence of HZ
During the study period, 22,250 incident cases of HZ were identified. Isolated complications were reported among 2.3% of all cases, including ophthalmologic complication (n = 360), otitis externa (n = 87), and nervous system complication (n = 63). During the study period, the annual incidence of HZ was 2.9 per 1,000, varying substantially with age, from less than 5 per 1,000 among individuals under 45 to more than 10 per 1,000 among the elderly.

Nested Case–Control Analysis
When the medical records of all HZ cases were examined, we identified 1,902 patients (8.5%) with a documented DM, 18 cases (0.1%) with AIDS, 213 cases (1.0%) with a history of lymphoma, and 60 cases (0.3%) with a history of leukemia. Table 1 describes the study cases and controls according to three age categories. In all age categories, HZ patients had higher proportion of individuals with a history of AIDS, DM, leukemia, and lymphoma compared to controls (Table 1).

In the multivariate analysis, a history of leukemia and lymphoma was associated with an increased risk of HZ with an OR of 3.55 (95% CI, 2.45–5.14) and 1.59 (CI, 1.35–1.87), respectively. Intake of steroids and antineoplastic agents was also associated with an OR of 1.80 (CI, 1.69–1.91) and 1.69 (CI, 1.47–1.95), respectively. The risk of HZ associated with leukemia varied significantly (p < 0.01) with age. The OR decreased from 9.06 (CI, 3.20–25.64) among patients 65 or above (Table 2). Similarly, the OR of HZ associated with antineoplastic medications and steroids was significantly lower with increasing age.

Individuals with diagnosed DM were at a significantly higher risk for HZ (OR = 1.53; CI, 1.44–1.62) compared to non-diabetics. When analyses were limited to individuals with documented DM, individuals under 45 with high levels (>8%) of Hba1c prior to the HZ outbreak had a significantly increased risk of HZ compared to patients with Hba1c level of less than 5%. No similar differences were observed in older ages (Table 2). For patients under 45 years, the HR for HZ associated with suffering DM for more than 3 years was 1.19 (95% CI: 0.62–2.29) and 0.70 (95% CI: 0.59–0.84) for patients aged ≥65 and the test for