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Family history of zoster and risk of developing herpes zoster

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ABSTRACT

Background: Studies have investigated a possible association between family history of HZ and the occurrence of HZ. However, the results were inconclusive and susceptible to bias. We evaluated this association in an elderly population.
Methods: The matched case-control study conducted at Kaiser Permanente Southern California in 2012-2015 included 656 incident HZ patients ≥60 whose skin lesion tested positive for varicella zoster virus by polymerase chain reaction. Half of the HZ patients were vaccinated with zoster vaccine as achieved by stratified sampling. The controls were randomly selected and 1:1 matched to the cases on sex, age (±1 year), and zoster vaccination (±3 months of the case's vaccination date). Conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI).
Results: Having any blood relative with a history of HZ was associated with a slightly increased risk of HZ (adjusted OR = 1.37, 95% CI 1.05–1.79). The adjusted OR associated with having one and two categories of first-degree blood relatives with a history of HZ was 1.30 (95% CI: 0.97–1.73) and 2.53 (95% CI: 1.17–5.44), respectively.
Conclusions: Our results suggested a weak association between the development of HZ and a positive family history of HZ among the elderly population.

Background

Herpes zoster (HZ), or shingles, is a painful vesicular rash, usually unilateral, caused by the varicella zoster virus (VZV). The pain and potential long-term effects associated with HZ, including post-herpetic neuralgia (PHN) and cranial nerve damage, can be debilitating, with a serious impact on quality of life. In 2006, the zoster vaccine received Food and Drug Administration (FDA) approval for use in healthy adults aged 60 and older. Zoster vaccine can increase cell-mediated immunity to VZV and reduce the risk of HZ (Tseng et al., 2011; Oxman et al., 2005).

Better understanding of risk factors for HZ can provide information about which patients are at an increased risk of HZ and could benefit most from vaccination. It can also provide insights regarding the pathophysiology of HZ and VZV reactivation. Multiple factors have been proposed as possibly associated with the risk of developing HZ. These include age, sex, race, genetics, immune disorders, physical trauma, psychological stress, toxin exposure, depression, and anxiety (Thomas and Hall, 2004; Schmader et al., 1990). Except for advanced age and immunosuppression, other risk factors for HZ are less clear. Family history has also been proposed as a potential risk factor for HZ, however, the findings are inconsistent (Ansar et al., 2014; Lasserre et al., 2012; Hernandez et al., 2011; Gatti et al., 2010; Hicks et al., 2008). Results from studies investigating genetic susceptibility to HZ have also been inconclusive (Crosslin et al., 2015; Wozniak et al., 2007; Cho et al., 2007; Opdal, 2004; Meenagh et al., 2002; Haanpaa et al., 2002).

Previous studies were prone to errors due to small sample size, unclear HZ case diagnosis, imprecise measurement of family history, differential recall between cases and controls, referral bias, and use of non-contemporaneous controls. To address these

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concerns, we conducted a prospective matched case-control study in a large health care organization in the United States.

Objectives

The aim of this study was to evaluate the association between a family history of HZ and the risk of developing HZ.

Study design

Setting

This study was conducted at Kaiser Permanente Southern California (KPSC), an integrated healthcare organization that provides prepaid comprehensive health care. KPSC serves more than 4.2 million members who are both racially and socio-economically diverse. The demographic makeup of the KPSC membership closely mirrors the Southern California population (Derose et al., 2013; Koebnick et al., 2012). Members receive medical care in KPSC-owned facilities and contracted facilities. Electronic health records store medical information such as socio-demographics, diagnoses, utilization (outpatient, emergency department, and inpatient encounters), procedures, laboratory tests, pharmacy utilization, vaccination records, membership history, and death.

Study population

The matched case-control study included incident HZ cases recruited from KPSC members, either with a history of vaccination with the HZ vaccine or without. An algorithm for recruitment was developed to achieve the matching. The algorithm started with identifying a vaccinated HZ case first, followed by an age (±2 years), and sex-matched unvaccinated HZ case, and then a vaccinated control matched to the vaccinated HZ case on age (±1 year), sex, and date of HZ vaccination (±3 months), and then an unvaccinated control age- (±1 year) and sex-matched to the unvaccinated case. The algorithm ensured an equal number of vaccinated and unvaccinated HZ cases in the case group that were 1:1 matched with vaccinated and unvaccinated control subjects. The number of cases and controls in the study was set to allow detection of an odds ratio associated with a family history of HZ as small as 1.5 with 80% power and a 5% type I error rate assuming 15% of control subjects reported a family history of HZ. The study was approved by KPSC Institutional Review Board and informed consent was obtained during the face-to-face visit for cases or during phone interviews for controls.

Cases

First, beginning from January 1, 2012, incident HZ patients at KPSC were identified prospectively every day by an ICD-9 code of 053.xx from outpatient and emergency department encounters. Patients with a zoster vaccine vaccination record (age $\geq$ 60 years at vaccination) between January 1, 2007 and June 30, 2014 and prior to HZ diagnosis were defined as the vaccinated HZ cases. On the same day or the day after the encounter with the HZ diagnosis, a trained research associate began contacting the vaccinated HZ patients by phone only to verify their HZ diagnosis and to arrange a face-to-face interview within 5 days of diagnosis and to obtain at least two separate skin lesion samples for testing. Up to 10 phone call attempts within 4 days after diagnosis per patient were made before the patient was considered ineligible. After obtaining informed consent, skin specimens were obtained according to the protocol prepared by the National VZV lab at the Centers for Disease Control and Prevention (CDC), which performed the standard polymerase chain reaction (PCR) test to confirm the presence of VZV from the skin specimens. Additional inclusion criteria to address feasibility concerns included selecting patients who were able to competently answer interview questions in English or Spanish, patients who resided in a safe and accessible area where the research associate could arrive in less than 3 hours of driving, and patients whose rash location was in an accessible area for specimen collection. A patient would not be included if he or she expressed concerns about being interviewed alone.

When the diagnosis of a vaccinated HZ case was confirmed by PCR at the CDC, a clinically diagnosed HZ case of the same sex and age (±2 year) with no record of zoster vaccination was identified from the daily list of HZ patients. The recruitment and inclusion criteria were identical to those of the vaccinated cases. If this unvaccinated case tested negative for VZV by PCR, then the process of identifying an unvaccinated matched HZ case would be repeated again until a positive one was found.

Controls

A vaccinated control subject was selected randomly from a list of KPSC members matched to a vaccinated HZ case on age (±1 year), sex, and date of zoster vaccine vaccination (±3 months) once the diagnosis of HZ of a vaccinated patient was confirmed by a PCR test. A control subject was considered eligible if the subject had never been clinically diagnosed with HZ. Up to 8 possible controls were identified to each case. Control subjects were contacted by a trained research associate for a telephone interview. Usually, the interview was conducted within 1 week after the eligibility was determined. Similarly, an unvaccinated control subject was selected randomly from a list to match to an unvaccinated HZ case on age (±1 year) and sex. Up to 3 phone call attempts per potential control were made before the next eligible control was considered.

Measurement

The cases received a face-to-face interview using a standardized questionnaire to obtain information on socio-demographic characteristics, family history of HZ, lifestyle factors, and comorbidities. The controls were interviewed by phone with the same structured questionnaire. For family history of HZ, the subjects were asked whether there were categories of relatives (parents, siblings, grandparents, children, grandchildren, uncle or aunt, cousin, and spouse) with a history of HZ and whether the relatives were blood related or non-blood related. The number of relatives in each relative category was not measured as this could significantly increase the difficulty of answering these questions among elderly patients and affect the validity.

The relatives with HZ were grouped into blood relative with HZ and non-blood relative with HZ. The number of subjects in the blood relative with HZ group included those who reported blood-related parents, siblings, grandparents, grandchildren, or uncle/aunt/cousin with a history of HZ. Furthermore, the blood relatives with HZ were also grouped by the number of subjects having 0, 1, 2, or 3 first order relative categories (parent, sibling, and children) with a history of HZ and by the number of subjects reporting any relatives other than first order (uncle/aunt, grandparent, grandchildren, cousin) with a history of HZ. The number of subjects who reported non-blood relative with a history of HZ included the ones having relatives who were not blood related (i.e. by marriage or by adoption) with a history of HZ, except for spouses with a history of HZ who were reported separately. The two non-blood relative categories were analyzed separately and served as "negative control" groups for interpretation of association.