MAYO CLINIC

BRIEF REPORT

Administrative Data to Explore the Role of Family History as a Risk Factor for Herpes Zoster

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Abstract

We used administrative data to study the impact of family history on the risk of herpes zoster (HZ). Our HZ cases and our HZ family history were both ascertained on the basis of medically attended diagnoses, without reliance on self-report or recall bias. Family history was associated with HZ risk among both siblings and parents. The strength of the association differed when the index child was latently infected with vaccine-strain vs wild-type varicella zoster virus.

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Varicella zoster virus (VZV) causes varicella and then establishes a latent infection. Years to decades later, VZV can reactivate to cause herpes zoster (HZ). Historically, by adulthood, virtually the entire population experienced varicella and was at risk of HZ, with approximately 1 million episodes of HZ now occurring in the United States annually.[1] Varicella vaccine, comprising attenuated vaccine-strain VZV (VS-VZV), was licensed in 1995. With uptake by school entry exceeding 90%, exposure to wild-type VZV (WT-VZV) has declined more than 95%.[2] While VS-VZV also establishes latency following varicella vaccination, the risk of HZ from VS-VZV is much lower than that from WT-VZV (ie, following varicella disease), and its manifestations may be milder too.[3,4]

Risk factors for HZ include age and immunosuppression, but these do not distinguish the approximately 30% of persons who experience HZ during their lives from those who do not.[1] Knowledge of HZ risk factors could elucidate mechanisms underlying VZV reactivation, help explain the epidemiology of HZ, and could lead to better prevention strategies. Genetic predisposition is a potential risk factor for HZ: several studies suggest that HZ risk is heritable; all relied on self-report and were subject to important biases.[5-10]

We used data from an administrative database to identify medically documented episodes of HZ. By defining proxy families in the database, we used these diagnosed HZ cases to categorize exposure (ie, HZ family history) when occurring in an index child in the family, and to categorize risk (ie, HZ episodes) when occurring in the index child's sibling or parent. By comparing HZ risk in siblings and parents when an index child did or did not experience HZ, we were able to generate estimates of the heritability of HZ risk. We evaluated heritability in families with VS-VZV–infected index children (ie, those who had been vaccinated) and in families with WT-VZV–infected index children (ie, those who had experienced varicella disease) separately, because the risks and manifestations of HZ from the 2 VZV strains appear to be different, potentially reflecting differences in the underlying biology or resulting in differences in case ascertainment.

METHODS

Our analytic approach and the disposition of study participants are portrayed in the Figure.

Data Source

Truven Health MarketScan Databases (1998-2014) include beneficiary and cobeneficiary data for millions of enrollees from public and private employers and health insurance plans.

Study Population

The sibling-sibling analysis included families having 2 or more children in which the oldest 2 were concordant for either WT-VZV or VS-VZV infection. The child-parent analysis included families having 1 or more children. The parent-spouse analysis included families

having 1 spouse (if >1 spouse, the oldest spouse), and having 1 or more children. We did not include continuous enrollment restrictions.

Study Definitions

- Family: primary beneficiary with his or her cobeneficiaries
- Family history: HZ in the index child during the period 1998 to 2014
- Child: cobeneficiary with birth (documented via *International Classification of Diseases, Ninth Revision* codes) during the period 1998 to 2014 (ie, maximum age, 16 years)
  - Index: the oldest child in the family
  - Sibling: the second oldest child in the family
- Parent: a primary beneficiary aged 18 to 64 years
- Spouse: the cobeneficiary of opposite sex aged 18 to 64 years
- HZ: defined using *International Classification of Diseases, Ninth Revision* codes (053.XX) during the period 1998 to 2014
- VS-VZV infected: defined using Current Procedural Terminology codes for varicella vaccination (90716, 90710) during the period 1998 to 2014
- WT-VZV infected: defined by absence of Current Procedural Terminology codes for varicella vaccination during the period 1998 to 2014

Data Analysis

We calculated relative risks (RRs) with corresponding 95% CI and *P* values for siblings and parents. We compared the exposed (with family history) vs the unexposed (without family history), that is, those with vs without history of HZ in the index child, respectively. We conducted separate analyses for families with index child having VS-VZV vs WT-VZV; siblings were matched to the index child by VZV strain and all parents were assumed to harbor WT-VZV. Family-specific behavioral factors (eg, recognizing and seeking health care for HZ) can cause spurious familial associations in HZ risk due to differential HZ ascertainment; to assess the impact of these artifacts, as a negative control (because parents and spouses were not genetically related), we compared HZ risk in spouses when parents did vs did not experience HZ, without regard to HZ in the index child.

RESULTS

Our results are presented in the Figure and in Tables 1 and 2. For siblings with vs without a family history of HZ (defined by HZ occurrence in the index child), the RR for HZ was 14.8 (95% CI, 6.2-35.9; $P<.001$). The RRs stratifying by VZV strain were 29.2 (95% CI, 4.0-211.9; $P=.03$) and 12.8 (95% CI, 4.8-34.2; $P<.001$) for WT-VZV and VS-VZV, respectively. This difference was not significant ($P=.46$).

For parents in families with vs without a family history of HZ, the RR for HZ was 3.3 (95% CI, 2.6-4.0; $P<.001$). The RRs stratifying by VZV strain in the index child were 6.3 (95% CI, 4.5-8.7; $P<.001$) and 2.1 (95% CI, 1.6-2.7; $P<.001$) for WT-VZV and VS-VZV, respectively. This difference was significant ($P<.001$).

For spouses of parents who did vs did not experience HZ, the RR for HZ was 2.5 (95% CI, 2.3-2.6; $P<.001$), whether or not the index child experienced HZ. Stratifying families by the VZV strain in the index child, the RRs in these spouses were 3.2 (95% CI, 2.8-3.7; $P<.001$) and 1.9 (95% CI, 1.8-2.1; $P<.001$), for WT-VZV and VS-VZ-VZV, respectively, providing an indication of the impact of nonheritable factors in our analyses.

We checked whether families stratified by VZV strain differed in parental age or in calendar years of observation, thereby biasing results. The median age of parents was similar (31 vs 32 years for WT-VZV and VS-VZV strata, respectively), and in the sibling analysis, the median year when observation time began (ie, birth of index child) was similar, too (2009 vs 2007 for WT-VZV and VS-VZV strata, respectively).

DISCUSSION

Several,[5-8] but not all,[9,10] reports suggest that the risk of HZ is heritable. However, previous HZ family history studies relied on survey methods prone to bias, and these studies showed no higher HZ association with first- vs second-degree relatives (ie, dose response).[6,8] We used administrative data to explore the heritability of HZ risk, restricting our analyses to documented, medically attended episodes of HZ. Our study complements survey-based studies,

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