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Increased Risk of Herpes Zoster in Children with Asthma: A Population-Based Case-Control Study

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Abstract

Objective—To determine the risk of herpes zoster (HZ) in children with or without asthma.

Study design—This study was designed as a population-based case-control study. We identified all children (age<18 years) with possible HZ in Olmsted County, MN, between 1996 and 2001 (n=306 identified by ICD codes and predetermined criteria for HZ) to identify true cases. To determine the association between asthma and HZ, we compared the frequency of asthma among children with HZ with that among birth date- and sex-matched corresponding controls (1:1 matching) who were Olmsted County, MN residents during the study period. Asthma was ascertained by predetermined criteria. A conditional logistic regression model was used to calculate odds ratio and 95% confidence interval.

Results—We identified 277 eligible HZ cases and of these 277 cases, 63 (23%) had a history of asthma prior to index date of HZ, whereas 35 of 277 matched controls (12.6%) had asthma (adjusted OR: 2.09, 95%CI: 1.24–3.52, p=0.006) adjusting for varicella vaccination and atopy status. Population-attributable risk percentage was 12%. Controlling for asthma and atopy status, varicella vaccination was associated with reduced risk of HZ (adjusted OR=0.44, 95% CI=0.21–0.92, p=0.028).

Conclusion—Asthma may be an unrecognized risk factor for reactivation of a non-airway related latent infection such as HZ in children.

Keywords

asthma; epidemiology; herpes zoster; shingles; varicella

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Shingles (herpes zoster, HZ) is a localized painful cutaneous eruption due to reactivation of varicella zoster virus (VZV) from a dormant state in dorsal root ganglia. There are about 1 million cases of HZ in the US each year, with an estimated lifetime attack rate of 30%. (1) But shingles is not limited to older adults. One third of cases occur before the age of 50 years, fewer than 10% are younger than age 20, and 5% are younger than the age 15 years. (2, 3) The majority of HZ cases (92%) occur in individuals without immunocompromising conditions. (2) Annual incidence of varicella was 1.2%–10.3% during the pre-varicella vaccine era. (4, 5)

Incidence of HZ has increased among all age groups from 3.2 per 1,000 person-years in 1996–1997 to 4.1 per 1,000 person-years in 2000–2001 in our study setting. (6) This is a significant increase compared with the incidence of HZ between 1945 and 1959, 1.3 per 1,000 person-years. (7) During the pre-varicella vaccine era, incidence of HZ among children had been reported to be in the range of 42 – 167 per 100,000 person-years; there have been rising trends of HZ incidence among children. (8, 9)

Reasons for these increases in HZ incidence are not understood fully; it is also unknown why some children acquire HZ and others do not, given that 86–93% of the US children aged 6–18 years had serologic evidence for previous varicella infection during the pre-varicella vaccine era. (10) We hypothesize that asthma might influence the risk of HZ given rising trends of asthma prevalence over the past few decades, (11) impact of asthma on risks of microbial infections, (12–14) and known suboptimal innate and adaptive immune functions in children with asthma. (15–17) Testing this hypothesis is important to understand the influence of asthma on susceptibility to non-airway related latent infection because most previous associations between asthma and infections were based on airway-related infections. To test this hypothesis, we conducted a population-based study in children who developed HZ between 1996 and 2001 and their matched controls.

METHODS

Olmsted County, Minnesota is an excellent setting to conduct a population-based epidemiologic study because medical care is virtually self-contained within the community (95%). Under auspices of Rochester Epidemiology Project (REP), each patient is assigned a unique identifier; all clinical diagnoses are electronically indexed, and essentially all medical care and providers are linked.

The study was designed as a population-based case-control study, which compared frequency of asthma among children with HZ with that among birthday-, sex-, and incident date-matched corresponding controls (1:1 individual matching) who had no previously diagnosed HZ. Index (incident) date for controls were closest clinic visit date (within one year) to index date of corresponding cases.

All incident cases with HZ among children between 1996 and 2001 were identified and eligibility and exclusion criteria were reported in detail. (6, 18) Briefly, potential HZ cases were identified from a broad search of diagnostic codes (International Classification of Diseases, Eighth Revision (ICD-8) codes 053.xx) for HZ and HZ complications. Medical records regarding each potential case were reviewed to verify that the case was indeed a new case of HZ based on criteria for HZ. Confirmation required that the child had a statement of characteristic rash (vesicular rash on dermatome), and signs or a statement of pain or itching at rash site in addition to a physician diagnosis of HZ. (6) Exclusion criteria included: (1) individuals without authorization for using medical records for research; (2) non-Olmsted County, Minnesota residents; or (3) another diagnosis explaining the rash such as culture positive for herpes simplex.

For each case of HZ, one control was randomly selected from matched individuals who had not developed HZ as of index date. Matched controls according to sex, date of birth (within 6 months), clinic registration year (within 1 year), and clinic visit within 1 year of index date of corresponding cases were randomly selected from the community. The literature showed that 86–93% of the US population aged 6–18 years had serologic evidence for previous varicella infection during the pre-varicella vaccine era (before 1995).(10) Thus, given the mean ($\pm$ SD) age of our subjects (9.8 ± 4.2 years) during the study period and low varicella vaccination rate during the study period (7.6% among children in the control group) due to a history of varicella or opt-out, controls were not required to have a history of varicella infection in the past.

We conducted comprehensive medical record reviews to apply predetermined criteria for asthma. These criteria have been extensively used in research for asthma epidemiology and were found to have high reliability.(11, 19, 20) Criteria are delineated in Table I. We included both definite and probable asthma according to criteria prior to index date of HZ cases because most children with probable asthma became definite over time.(11) Information of clinical factors and potential confounders pertinent to this study were collected from medical records summarized in Table II.

Statistical analyses

Matched analysis via conditional logistic regression was used to test for associations with HZ for asthma prior to index date and other factors. To further evaluate the association between HZ and the primary risk factor of interest, prior asthma was carried forward into a multivariable model along with any other factors detected as significant ($P < .05$) from univariate modeling. For the subgroup with a history of varicella but without a documented varicella vaccination, regular logistic regression was used to test for associations with HZ because the exclusion of various cases and controls left the subset essentially unmatched. We calculated the population attributable risk percent (PAR%) of asthma for HZ which was calculated by using the following formula, $P(OR-1)/[1+P(OR-1)]$, where P is the prevalence of asthma in the population and OR is matched odds ratio. We estimated the incidence of HZ among children in the study time frame, with rates adjusted for age and sex by direct standardization against the 2000 US population. We computed the rate of age-appropriate general medical examination (ie, well-child exam) over time among children with and without asthma, expressed as the number of events per one person-year, and formally tested for a group difference using Poisson regression.

RESULTS

A total of 277 eligible HZ cases were identified, of whom 47.3% were male, 92.0% were white, and the mean age at diagnosis of HZ was 9.8 years. The characteristics of HZ cases, as well as the matched controls, are summarized in Table II. As expected, a higher proportion of HZ cases had documentations on a history of varicella infection (chicken pox) in the past compared with controls (54% vs. 22%, $P < 0.001$). Neither a history of varicella infection in the past (85% for children with asthma vs. 83% for children without asthma, $p = 0.67$) nor varicella vaccinations (11% vs. 10%, respectively, $p = 0.78$) was associated with asthma status. In all, 55 (9.9%) of the 554 children were documented as having a varicella vaccine prior to the index HZ date, and the remaining 499 (90.1%) had no documentation of a past varicella vaccine. Varicella vaccine was originally recommended for children 12–15 months of age; very few of our cases between 1996 and 2001 would have been expected to be vaccinated.

The incidence of HZ in children

The incidence of HZ in children is summarized in Table III. The overall age- and sex-adjusted annual incidence of HZ was 141 (124–157) per 100,000 during the study period. Broken down by sex- and age-adjusted annual incidence of HZ was 152 (95% CI, 128–177) per 100,000 females and 129 (95% CI, 107–152) per 100,000 males. The sex-adjusted annual incidence rates of HZ (per 100,000) in groups of children aged 0–6 years, 7–12 years, and 13–17 years were 81, 197, and 150, respectively.

Asthma and HZ

The summarized results for the association between asthma and HZ are found in Table 2 and IV. Sixty-three (22.7%) of the 277 cases had asthma prior to index date of HZ, compared with 35 (12.6%) of the 277 controls (unadjusted OR: 2.17, 95% CI: 1.34–3.51, $p=0.002$). Adjusted for varicella vaccination history and atopy status, a prior history of asthma was significantly associated with increased risk of HZ (adjusted OR: 2.09, 95% CI: 1.24–3.52, $p=0.006$). The results based on a multivariate model are summarized in Table IV. Based on these data, the population attributable risk percent of asthma for risk of HZ was estimated to be 12%. Compared with children without asthma, the risk of HZ was marginally to significantly higher for children with asthma in each of the three stages of remission (ie, in remission, not in remission, and current asthma). In the subset of those with a history of varicella infection but without a documented varicella vaccination ($n=203$), asthma had a similar estimate of effect on risk of HZ, albeit not statistically significant, controlling for age, sex, registration year, and index date (adjusted OR: 2.11, 95% CI: 0.91–4.93, $p=0.084$). Inhaled corticosteroids were not associated with the risk of asthma (OR: 1.33, 95% CI: 0.32 – 5.52, $p=0.691$) and none of the children with asthma received systemic corticosteroid within 3 months of the index date of HZ.

Atopy status was defined as the presence of sensitization against aeroallergen or food allergen and was associated with an elevated risk of HZ (unadjusted OR: 3.00, 95% CI: 1.09–8.25, $p=0.033$) from univariate analysis, but was not significant after adjusting for asthma and varicella vaccination history in the multivariable model. Although not statistically significant, a family history of asthma in first-degree relatives was suggestive of an increased risk of HZ (unadjusted OR: 1.42, 95% CI: 0.91–2.22, $p=0.119$) in the univariate modeling.

Other variables and HZ

Children with a documented varicella immunization prior to index HZ date had a reduced risk of HZ (adjusted OR=0.44, 95% CI=0.21–0.92, $p=0.028$) compared with non-immunized children, controlling for asthma and atopy status. Ethnicity, maternal educational level, a history of recent trauma in the affected dermatome, co-morbid conditions, and smoking exposure at home were not significantly associated with risk of HZ.

DISCUSSION

We found that a history of asthma was significantly associated with an increased risk of HZ in children. The population-attributable risk percent for asthma in all subjects was 12%, suggesting that approximately 12% of the disease burden of HZ could be attributable to asthma at a population level. Thus, this report potentially expands the impact of asthma to include a non-airway related infection.

The incidence of HZ in our study was within the range of reported incidence rates of HZ among children during the pre-vaccine era (30–220 per 100,000 person-years)(21, 22) depending on age and regions, although none of these incidence rates were standardized as

were ours. In addition, the prevalence of asthma in our study subjects (17.7%) is similar to that of a population-based study in our community (17.6%) among children in grades kindergarten through 12.(23) Our study results showed a strong association between asthma and risk of HZ (adjusted OR: 2.09, 95% CI: 1.24–3.52, $p=0.006$), suggesting that asthma may be a significant yet unrecognized risk factor for non-airway related latent infection such as HZ. Our study results are unlikely to be due to a detection bias, which arises when exposure status affects the probability of outcome detection (because children with asthma might seek medical care more likely than those without asthma). This is because HZ is considered a significant clinical condition in children, and parental decision to seek medical evaluation is minimally (or not) influenced by asthma or atopic status. We also assessed the frequency of age-appropriate general medical evaluation (ie, well-child exam) during the study period between children with and without asthma in this study. The frequency of well-child exams in children with asthma (0.22, 95% CI: 0.19–0.27 per person-year) were slightly lower than that for children without asthma (0.26, 95%CI: 0.24–0.28 per person year), but this difference was not statistically significant (OR: 0.85, 95%CI: 0.71–1.03, $p=0.087$), suggesting that asthma status may not affect access to medical care. Along these lines, we previously reported similar health care utilizations between children with and without asthma and found no differences in risk of outcome events between children with asthma with and without a physician diagnosis of asthma in our study setting. (24, 25) Although we could not verify a history of varicella infection in the past for all controls, the literature suggested 86%–93% of children aged 6–18 years had serologic evidence of varicella infection in the United States during the pre-varicella vaccine era (before 1995)(10) and the mean ($\pm$ SD) age of our study subjects was 10 ($\pm$ 4.2) years of age during the study period (1996–2001). Thus, most of our control subjects were likely to have varicella infection and the proportions of children who had not been immunized with varicella vaccine during the study period might reflect a history of varicella infection (87–92%). When we limited the analysis to those with a history of varicella infection without varicella vaccination, the estimated effect of asthma was similar (adjusted OR: 2.11, 95%CI: 0.91–4.93, $p=0.084$) despite not reaching statistical significance. Neither a history of varicella infection in the past nor varicella vaccination was associated with asthma suggesting a history of varicella infection and vaccination are likely to result in non-differential misclassification bias. Finally, asthma medications did not account for the association because none of children with asthma received systemic corticosteroids within 3 months of the index date and inhaled corticosteroid (ICS) were not associated with the risk of HZ—consistent with the literature. (26) Although a recent study showed increased risk of HZ among patients with COPD who used ICS,(27) this study was susceptible to detection bias because it did not fully address differential health care access between cases and control. Asthma remission status (or disease activity) did not seem to differentially influence risk of HZ because the 95% confidence interval among the groups of children with remission, those without remission, and those with current asthma were overlapped. The impact of asthma on the risk of HZ appears be independent of atopic sensitization, although it was significantly associated with the risk of HZ in univariate analysis. Earlier clinical studies suggested that asthma is associated with increased risk of HZ. (28, 29) However, these studies were limited because assessment of the association between asthma and risk of HZ was not their primary study aim, asthma ascertainment was based on ICD codes, and there were no well-defined concurrent control groups for comparisons.

The potential biological mechanisms underlying the association between asthma and the risk of HZ are unknown. Because the majority of adults age 40 years or older (99.5%) have serologic evidence for past varicella zoster infection,(6) and the risk of HZ has been known to be associated with aging, cell-mediated immunity (CMI) is a crucial immune function protecting humans from HZ.(30) The literature suggests that individuals with asthma or other atopic conditions may have an impaired innate and adaptive immunity.(15–17) Atopic

dermatitis has been reported to be associated with suboptimal cell-mediated immune response to herpes simplex virus. (31) Therefore, we postulate that immunogenetic factors associated with asthma might result in impairment of cell-mediated immune functions leading to an increased risk of HZ. Further studies are needed to identify the underlying mechanisms.

A noteworthy finding in our study includes the favorable effect of varicella vaccination on the risk of HZ (adjusted OR=0.44, 95% CI=0.21–0.92, $p=0.028$), although it was based on a small number of children vaccinated because varicella vaccine was introduced in 1995. There is paucity in data concerning the vaccine effectiveness against HZ in children. A previous study based on children age 12 years or younger suggested a protective effect of varicella vaccine on risk of HZ. (28)

The strengths of our study include epidemiologic advantages of a self-contained health care environment with a unified medical record system for research. Additional strengths were a population-based case-control study and predetermined criteria for asthma, which were extensively used in previous studies. We designed this study as an incidence density case control study, which allows controls to become cases during the study period. This approach makes parameter estimates of odds ratios closer to risk ratios. However, there are inherent limitations in the study due to its retrospective design. Asthma ascertainment in our study was based on the retrospective criteria for asthma but these criteria were extensively used in previous studies concerning asthma epidemiology and found to have high reliability.(20) We could not assess asthma control or severity status based on self-reported asthma symptoms. Instead, we assessed asthma remission status. Also, the residents of Olmsted County, Minnesota were predominantly Caucasian; this limits generalizability of our findings to other ethnic groups. However, asthma prevalence among controls in our study (12.6%) was similar to the national average (9.6–13%)^{31, 32} and at the cost of generalizability, this ethnically homogeneous population may minimize a confounding effect of ethnicity and socioeconomic status (and its related risk factors). Ascertainment of HZ was based on a physician diagnosis and predetermined retrospective criteria. Similarly, although our criteria for asthma has been extensively used for epidemiologic and laboratory studies in the past, it should be subject to non-differential misclassification with regard to outcome event (incidence of HZ).

In conclusion, asthma may be an unrecognized risk factor for non-airway related latent infection such as HZ in children. These findings need to be replicated and mechanisms underlying this association need to be studied.

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Abbreviations

HZ Herpes zoster

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Table 1**Definition of Asthma**

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:

- 1** History of cough, dyspnea, and/or wheezing, OR history of cough and/or dyspnea plus wheezing on examination,
- 2** Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and
- 3** Two or more of the following:
 - Sleep disturbance by nocturnal cough and wheeze
 - Nonsmoker (14 yrs or older)
 - Nasal polyps
 - Blood eosinophilia higher than 300/uL
 - Positive wheal and flare skin tests OR elevated serum IgE
 - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests showing one FEV₁ or FVC less than 70% predicted and another with at least 20% improvement to an FEV₁ of higher 70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV₁
 - Favorable clinical response to bronchodilator

Table 2

Characteristics of Herpes Zoster (HZ) for Cases and Control Subjects and Factors Associated with Risk of HZ in Children Based on Matched Analysis

Variables	Control (n = 277)	Case (n = 277)	Odds ratios for HZ (95% CI), <i>p</i> -value
Age at case's index date (mean $\pm$ SD, yr)	9.8 $\pm$ 4.2	9.8 $\pm$ 4.2	1.25 (0.77 – 2.04), 0.363
Sex, female	146 (52.7%)	146 (52.7%)	-
Ethnicity, white	238/264 (90.2%)	240/261 (92.0%)	1.26 (0.69 – 2.31), 0.447
Maternal educational status *			
<High School	9 (7.2%)	14 (11.1%)	<i>Referent</i>
High School Graduate	36 (28.8%)	37 (29.4%)	1.51 (0.58 – 3.95), 0.395
Some College	59 (47.2%)	59 (46.8%)	1.56 (0.63 – 3.87), 0.342
College Graduate	21 (16.8%)	16 (12.7%)	2.04 (0.71 – 5.90), 0.187
A family history of asthma 1st-degree relatives	45 (16.2%)	59 (21.3%)	1.42 (0.91 – 2.22), 0.119
A history of asthma prior to index date	35 (12.6%)	63 (22.7%)	2.17 (1.34 – 3.51), 0.002
Remission status of asthma at index date			
No asthma prior to index date	242 (87.4%)	214 (77.2%)	<i>Referent</i>
Asthma in remission **	6 (2.2%)	15 (5.4%)	3.33 (1.17 – 9.43), 0.024
Asthma not in remission	9 (3.2%)	16 (5.7%)	2.29 (0.95 – 5.54), 0.067
Current Asthma	20 (7.2%)	32 (11.5%)	1.86 (1.02 – 3.38), 0.042
Atopic status defined as aeroallergen or food allergen sensitization	5 (1.8%)	15 (5.4%)	3.00 (1.09 – 8.25), 0.033
Varicella vaccination before the index date	34 (12.3%)	21 (7.6%)	0.48 (0.24 – 0.96), 0.037
Tobacco smoke exposure at index date	14 (5.1%)	17 (6.1%)	1.21 (0.60 – 2.46), 0.591
Regular use of inhaled corticosteroids	3 (8.6%)	7 (11.1%)	1.33 (0.32 – 5.52), 0.691
The presence of comorbidities before the index date ***	23 (8.3%)	25 (9.0%)	1.10 (0.60 – 2.02), 0.758
Mechanical trauma in the affected dermatome within 1 month prior to the index date	1 (0.4%)	3 (1.1%)	3.00 (0.31 – 28.84), 0.341
Determined psychological, social and behavioral problem prior to index date	28 (10.1%)	27 (9.7%)	0.96 (0.54 – 1.70), 0.884

The proportions of subjects under each variable were calculated based on available data excluding missing data;

* an unmatched analysis was performed via regular logistic regression due to extensive missing data for this variable;

** Asthma remission was defined as the absence of asthma symptoms, no use of asthma medication, no clinic or ED visit or no hospitalization for asthma 3 year or longer prior to the index date; Asthma not in remission was defined as the presence of the above asthma-related events between one and three years prior to index date of HZ; Current asthma was defined as the presence of asthma symptoms, use of asthma medication, or clinic or ED visit within the past 1 year prior to the index of HZ;

*** Comorbid conditions were based on the Advisory Committee on Immunization Practices–recommended pneumococcal vaccine–eligible conditions

Estimated Annual Incidence Rate* of Herpes Zoster During the Study Period with Age- and Sex-Adjusted Based on the 2000 US Census

Table III

Age group (yrs)	1996 – 1997			1998 – 1999			2000 – 2001		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0–6	70.2	57.2	63.8	78.3	131.8	104.4	70.0	82.1	75.9
7–12	88.9	160.5	123.6	156.1	302.1	227.1	253.0	221.6	237.7
13–17	135.1	94.5	115.3	179.0	111.0	145.9	159.0	210.4	184.0
Total	95.2	103.6	99.3	134.0	185.0	158.8	158.9	167.1	162.8

Per 100,000 population; Adjusted for age and sex based on the 2000 US Census.

Table IV

Association between asthma and risk of HZ based on a multivariable conditional logistic regression model

	* Adjusted odds ratios	95% confidence interval	P-values
A history of asthma prior to index date	2.09	1.24–3.52	0.006
Atopic status defined as aeroallergen or food allergen sensitization	0.97	0.88–1.07	0.53
Varicella vaccination before the index date	0.44	0.21–0.92	0.028

* Individual matching factors including age, sex, registration year, and index date were not adjusted