

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

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

Study design This study was designed as a population-based case-control study. We examined all children (aged <18 years) with possible HZ in Olmsted County, Minnesota, between 1996 and 2001 (n = 306; identified by *International Classification of Diseases, Eighth Revision* 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 age- and sex-matched corresponding controls (1:1 matching) who resided in Olmsted County, Minnesota, during the study period. Asthma was ascertained based on predetermined criteria. A conditional logistic regression model was used to calculate ORs and 95% CIs.

Results We identified 277 eligible patients with HZ, 63 (23%) of whom had a history of asthma before the index date of HZ, compared with 35 of 277 (12.6%) matched controls (aOR, 2.09; 95% CI, 1.24-3.52; $P = .006$), adjusting for varicella vaccination and atopy status. The population-attributable risk percentage was 12%. Controlling for asthma and atopy status, varicella vaccination was associated with reduced risk of HZ (aOR, 0.44; 95% CI, 0.21-0.92; $P = .028$).

Conclusion Asthma may be an unrecognized risk factor for reactivation of a non-airway-related latent infection such as HZ in children. (*J Pediatr* 2013; ■: ■- ■).

Herpes zoster (HZ), or shingles, is a localized painful cutaneous eruption due to reactivation of varicella zoster virus from a dormant state in dorsal root ganglia. Approximately 1 million cases of HZ occur in the US each year, with an estimated lifetime attack rate of 30%.¹ HZ is not limited to older adults, however; one-third of affected patients are aged <50 years, 10% are aged <20 years, and 5% are aged <15 years.^{2,3} The majority of HZ cases (92%) involve individuals without an immunocompromising condition.² The annual incidence of varicella was 1.2%-10.3% during the pre-varicella vaccine era.^{4,5}

The incidence of HZ has increased in all age groups in our study setting, from 3.2 per 1000 person-years in 1996-1997 to 4.1 per 1000 person-years in 2000-2001.² This is a significant increase compared with the recorded incidence of 1.3 per 1000 person-years for 1945-1959.⁶ There is a trend toward an increasing incidence of HZ in children compared with the recorded pre-varicella vaccine era incidence of 42-167 per 100 000 person-years.^{7,8}

The reasons for the increased HZ incidence are not completely understood. It is also unknown why some children acquire HZ and others do not, given that 86%-93% of US children aged 6-18 years had serologic evidence of previous varicella infection during the pre-varicella vaccine era.⁹ We hypothesize that asthma might influence the risk of HZ given rising trends of asthma prevalence over the past few decades,¹⁰ impact of asthma on risks of microbial infections,¹¹⁻¹³ and known suboptimal innate and adaptive immune functions in children with asthma.¹⁴⁻¹⁶ 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 matched controls.

Methods

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

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HZ Herpes zoster

The study was designed as a population-based case-control study, to compare the frequency of asthma in children with HZ and age-, sex-, and incident date-matched corresponding controls (1:1 individual matching) without previously diagnosed HZ. The index (incident) date for controls was the closest clinic visit date (within 1 year) to the index date of the corresponding cases.

All incident cases of HZ in children between 1996 and 2001 were identified. Eligibility and exclusion criteria have been reported in detail previously.^{2,17} In brief, potential cases of HZ were identified from a broad search of diagnostic codes (*International Classification of Diseases, Eighth Revision* codes 053.xx) for HZ and HZ complications. Medical records for each potential case were reviewed to verify that the case was indeed a new case of HZ based on criteria for HZ. Confirmation required a characteristic rash (ie, vesicular rash on a dermatome) and signs or symptoms of pain or itching at the rash site in addition to a physician's diagnosis of HZ.² Exclusion criteria included lack of authorization for the use of medical records for research, nonresidence in Olmsted County, Minnesota, and another diagnosis possibly explaining the rash, such as a culture positive for herpes simplex.

For each case of HZ, 1 control was randomly selected from matched individuals who had not developed HZ as of the index date. Controls matched according to sex, date of birth (within 6 months), year of clinic registration (within 1 year), and clinic visit within 1 year of the index date of corresponding cases were selected at random from the community. According to the literature, during the pre-varicella vaccine era (before 1995), 86%-93% of the US population aged 6-18 years had serologic evidence of previous varicella infection.⁹ Thus, given the mean age of our patients (9.8 ± 4.2 years) and low varicella vaccination rate during the study period (7.6% in the control group), owing to a history of varicella or opt-out, controls were not required to have a history of previous varicella infection.

We conducted comprehensive medical record reviews to apply predetermined criteria for asthma. These criteria have been used extensively in asthma epidemiology research and were found to have high reliability.^{10,18,19} Criteria are delineated in **Table I**. We included both definite and probable asthma according to criteria before the index date of HZ cases, because most children with probable asthma became definite over time.¹⁰ Information on clinical factors and potential confounders pertinent to this study were collected from medical records, as summarized in **Table II**.

Statistical Analyses

We used matched analysis via conditional logistic regression to test for associations with HZ for asthma before the index date and other factors. To further evaluate the association between HZ and the primary risk factor of interest, we carried forward previous asthma into a multivariate model, along with any other factors identified as significant ($P < .05$) on univariate modeling. For the subgroup of patients with a history of varicella but without a documented varicella vaccination, we used regular logistic regression to test for

Table I. Definition of asthma

A patient was considered to have definite asthma if a physician diagnosed asthma and/or if each of the following 3 conditions were present, and was considered to have probable asthma if only the first 2 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 longer when symptoms were absent
3. Two or more of the following:
 - Sleep disturbance by nocturnal cough and wheeze
 - Nonsmoker (age ≥ 14 y)
 - Nasal polyps
 - Blood eosinophilia (eosinophils $>300/\mu\text{L}$)
 - Positive wheal and flare skin tests or elevated serum IgE
 - History of hay fever, infantile eczema, or regular cough, dyspnea, and wheezing on exposure to an antigen
 - Pulmonary function tests showing a FEV_1 or forced vital capacity value $<70\%$ of predicted and another with at least a 20% improvement to an FEV_1 of $>70\%$ predicted or a methacholine challenge test showing a $\geq 20\%$ decrease in FEV_1
 - Favorable clinical response to bronchodilator

FEV_1 , forced expiratory volume in 1 second.

associations with HZ, because the exclusion of various cases and controls left the subset essentially unmatched. We calculated the population-attributable risk percent of asthma for HZ using the following formula: $P(\text{OR} - 1)/[1 + P(\text{OR} - 1)]$, where P is the prevalence of asthma in the population and OR is matched OR . We estimated the incidence of HZ in children during the study period, and adjusted rates for age and sex by direct standardization against the 2000 US population. We computed the rate of age-appropriate general medical examinations (ie, well-child exams) over time in children with and without asthma, expressed as the number of events per 1 person-year, and formally tested for a between-group difference using Poisson regression.

Results

A total of 277 eligible patients with HZ were identified, of whom 47.3% were male, and 92.0% were white. The mean age at diagnosis of HZ was 9.8 years. Characteristics of the patients with HZ and matched controls are summarized in **Table II**. As expected, the proportion of patients with a documented history of varicella infection (chickenpox) was higher in the HZ group compared with controls (54% vs 22%; $P < .001$). Neither a history of previous varicella infection (85% in children with asthma vs 83% in those without asthma; $P = .67$) nor previous varicella vaccination (11% vs 10%, respectively; $P = .78$) was associated with asthma status. In all, 55 of the 554 children (9.9%) had a documented varicella vaccine before the index HZ date, whereas the remaining 499 (90.1%) did not. The varicella vaccine was originally recommended for children aged 12-15 months, and, thus, we expected that very few of our cases between 1996 and 2001 would have been vaccinated.

Incidence of HZ in Children

The incidence of HZ in children is summarized in **Table III**. The overall age- and sex-adjusted annual incidence during

Table II. Characteristics of HZ for cases and controls and factors associated with risk of HZ in children based on matched analysis

Variables	Controls (n = 277)	Cases (n = 277)	OR for HZ (95% CI); P value
Age at case's index date, years, mean $\pm$ SD	9.8 $\pm$ 4.2	9.8 $\pm$ 4.2	1.25 (0.77-2.04); .363
Female sex, n (%)	146 (52.7)	146 (52.7)	-
White ethnicity, n (%)	238/264 (90.2)	240/261 (92.0)	1.26 (0.69-2.31); .447
Maternal educational status, n (%) [*]			
Non-high school graduate	9 (7.2)	14 (11.1)	Referent
High school graduate	36 (28.8)	37 (29.4)	1.51 (0.58-3.95); .395
Some college	59 (47.2)	59 (46.8)	1.56 (0.63-3.87); .342
College graduate	21 (16.8)	16 (12.7)	2.04 (0.71-5.90); .187
History of asthma in first-degree relatives, n (%)	45 (16.2)	59 (21.3)	1.42 (0.91-2.22); .119
History of asthma before the index date, n (%)	35 (12.6)	63 (22.7)	2.17 (1.34-3.51); .002
Remission status of asthma at index date, n (%)			
No asthma before index date	242 (87.4)	214 (77.2)	Referent
Asthma in remission [†]	6 (2.2)	15 (5.4)	3.33 (1.17-9.43); .024
Asthma not in remission	9 (3.2)	16 (5.7)	2.29 (0.95-5.54); .067
Current asthma	20 (7.2)	32 (11.5)	1.86 (1.02-3.38); .042
Atopic status (aeroallergen or food allergen sensitization), n (%)	5 (1.8)	15 (5.4)	3.00 (1.09-8.25); .033
Varicella vaccination before index date, n (%)	34 (12.3)	21 (7.6)	0.48 (0.24-0.96); .037
Tobacco smoke exposure at index date, n (%)	14 (5.1)	17 (6.1)	1.21 (0.60-2.46); .591
Regular use of inhaled corticosteroids, n (%)	3 (8.6)	7 (11.1)	1.33 (0.32-5.52); .691
Presence of comorbidities before index date, n (%) [‡]	23 (8.3)	25 (9.0)	1.10 (0.60-2.02); .758
Mechanical trauma in affected dermatome within 1 month before index date, n (%)	1 (0.4)	3 (1.1)	3.00 (0.31-28.84); .341
Psychological, social, or behavioral problem before index date, n (%)	28 (10.1)	27 (9.7)	0.96 (0.54-1.70); .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 owing 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 emergency department visit, or no hospitalization for asthma for at least 3 years before the index date of HZ. Asthma not in remission was defined as the presence of the foregoing asthma-related events between 1 and 3 years before the index date of HZ. Current asthma was defined as the presence of asthma symptoms, use of asthma medication, or clinic or emergency department visit within 1 year before the index date of HZ.

[‡]Comorbid conditions were based on the Advisory Committee on Immunization Practices–recommended pneumococcal vaccine–eligible conditions.

the study period of HZ was 141 (95% CI, 124-157) per 100 000, including 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) were 81 in children aged 0-6 years, 197 in those aged 7-12 years, and 150 in those aged 13-17 years.

Asthma and HZ

Results for the association between asthma and HZ are summarized in **Tables II** and **IV**. Sixty-three of the 277 cases (22.7%) had asthma before the index date of HZ, compared with 35 of the 277 controls (12.6%) (unadjusted OR, 2.17; 95% CI, 1.34-3.51; $P = .002$). After adjustment for varicella vaccination history and atopy status, a previous history of asthma was significantly associated with increased risk of HZ (aOR, 2.09; 95% CI, 1.24-3.52; $P = .006$). 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 as 12%. Compared with children without asthma, children with asthma had a marginally to significantly greater risk of HZ in each of the 3 stages of remission (ie, in remission, not in remission, and current asthma). In the subset of patients with a history of varicella infection but without a documented varicella vaccination ($n = 203$), asthma had a similar estimated effect on the risk of HZ (albeit not statistically significant) after controlling for age, sex, registration year, and index date (aOR, 2.11; 95% CI, 0.91-4.93; $P = .084$). Use of inhaled corticosteroids was not associated with the risk of asthma (OR, 1.33; 95% CI, 0.32-5.52; $P = .691$), and none of the children with asthma received a systemic corticosteroid within 3 months of the index date of HZ.

Atopy status, defined as the presence of sensitization against an aeroallergen or a food allergen, was associated with an elevated risk of HZ (unadjusted OR, 3.00; 95% CI,

Table III. Estimated annual incidence rate^{*} of HZ during the study period, age- and sex-adjusted based on the 2000 US Census

Age group, y	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 multivariate conditional logistic regression model

	aOR [*]	95% CI	P value
A history of asthma before the index date	2.09	1.24-3.52	.006
Atopic status (aeroallergen or food allergen sensitization)	0.97	0.88-1.07	.53
Varicella vaccination before the index date	0.44	0.21-0.92	.028

^{*}Adjustment did not include individual matching factors, including age, sex, registration year, and index date.

1.09-8.25; $P = .033$) on univariate analysis, but was not significant after adjusting for asthma and varicella vaccination history in the multivariate 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; $P = .119$) in the univariate modeling.

Other Variables and HZ

Children with a documented varicella immunization before the index HZ date had a reduced risk of HZ (aOR, 0.44; 95% CI, 0.21-0.92; $P = .028$) compared with nonimmunized children, after controlling for asthma and atopy status. Ethnicity, maternal educational level, history of recent trauma in the affected dermatome, comorbid conditions, and smoking exposure at home were not significantly associated with the 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 percentage 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 the present study is within the range of reported incidence rates of HZ in children during the pre-varicella vaccine era (30-220 per 100 000 person-years),^{20,21} depending on age and regions, although unlike ours, none of those incidence rates was standardized. In addition, the prevalence of asthma in our study subjects (17.7%) is similar to that reported in a population-based study of grade K-12 children in our community (17.6%).²² Our data show a strong association between asthma and the risk of HZ (aOR, 2.09; 95% CI, 1.24-3.52; $P = .006$), suggesting that asthma may be a significant, yet unrecognized, risk factor for non-airway-related latent infections, such as HZ.

Our study results are not likely related to a detection bias, which arises when exposure status affects the probability of outcome detection (because children with asthma might be more likely to seek medical care than those without asthma). This is because HZ is considered a significant clinical condition in children, and parents' decision to seek medical evaluation is not influenced or only minimally influenced by asthma or atopic status.

We also compared the frequency of age-appropriate general medical evaluation (ie, well-child exam) in children with and without asthma during the study period. The frequency of well-child exams in children with asthma (0.22 per person-year; 95% CI, 0.19-0.27) was slightly lower than that in children without asthma (0.26 per person-year; 95% CI, 0.24-0.28), but the difference was not statistically significant (OR, 0.85; 95% CI, 0.71-1.03; $P = .087$), suggesting that asthma status might not affect access to medical care. Along these lines, we previously reported similar health care utilization

in children with and without asthma and found no differences in the risk of outcome events in our study setting.^{23,24}

Although we could not verify a history of previous varicella infection for all controls, the literature suggests that 86%-93% of children aged 6-18 years had serologic evidence of varicella infection in the US during the pre-varicella vaccine era (before 1995),⁹ and the mean age of our study subjects was 10 ± 4.2 years during the study period (1996-2001). Thus, most of our control subjects likely had varicella infection, and the proportion 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 children with a history of varicella infection without varicella vaccination, the estimated effect of asthma was similar (aOR, 2.11; 95% CI, 0.91-4.93; $P = .084$), despite not reaching statistical significance. Neither a history of previous varicella infection nor varicella vaccination was associated with asthma, suggesting that a history of varicella infection and vaccination are likely to result in nondifferential misclassification bias.

Finally, asthma medications did not account for the association, given that none of the children with asthma received systemic corticosteroids within 3 months of the index date, and inhaled corticosteroid use was not associated with the risk of HZ, consistent with the literature.²⁵ Although a recent study reported an increased risk of HZ in patients with chronic obstructive pulmonary disease who used inhaled corticosteroids,²⁶ that study was susceptible to detection bias, because it did not fully address differential health care access between cases and controls.

Asthma remission status (or disease activity) did not seem to differentially influence the risk of HZ, with overlapping 95% CIs in the children with remission, those without remission, and those with current asthma. The impact of asthma on the risk of HZ appears to be independent of atopic sensitization, although it was significantly associated with the risk of HZ on univariate analysis. Earlier clinical studies suggested that asthma is associated with an increased risk of HZ^{27,28}; however, those studies were limited by several factors, including that assessing the association between asthma and risk of HZ was not the primary study aim, asthma ascertainment was based on *International Classification of Diseases, Eighth Revision* codes, and there were no well-defined concurrent control groups for comparison.

The potential biological mechanisms underlying the association between asthma and the risk of HZ are unknown. Because the majority of adults aged ≥ 40 years (99.5%) exhibit serologic evidence of past varicella zoster infection,⁶ and the risk of HZ has been known to be associated with aging, cell-mediated immunity is a crucial immune function protecting humans from HZ.²⁹ The literature suggests that individuals with asthma or other atopic conditions may have impaired innate and adaptive immunity.¹⁴⁻¹⁶ Atopic dermatitis is reportedly associated with suboptimal cell-mediated immune

response to herpes simplex virus.³⁰ Thus, we postulate that immunogenetic factors associated with asthma might result in impaired cell-mediated immune function, leading to an increased risk of HZ. Further studies are needed to identify the underlying mechanisms.

A noteworthy finding of the present study includes the favorable effect of varicella vaccination on the risk of HZ (aOR, 0.44; 95% CI, 0.21-0.92; $P = .028$), although this finding is based on only a small number of children vaccinated, given that varicella vaccine was introduced in 1995. There is a paucity of data on the vaccine's effectiveness against HZ in children. A previous study of children aged ≤ 12 years suggested a protective effect of varicella vaccine against the risk of HZ.²⁷

Strengths of the present study include the epidemiologic advantages of a self-contained health care environment with a unified medical record system for research, along with the population-based case-control study design and predetermined criteria for asthma, which have been used extensively 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 ORs closer to risk ratios. Nevertheless, this study has some inherent limitations owing to its retrospective nature. Asthma ascertainment was based on retrospective criteria for asthma, which have been used in previous studies on asthma epidemiology and found to have high reliability.¹⁹ We could not assess asthma control or severity status based on self-reported asthma symptoms; instead, we assessed asthma remission status. Moreover, the residents of Olmsted County, Minnesota, were predominantly Caucasian, which limits the generalizability of our findings to other ethnic groups. However, the prevalence of asthma in our controls (12.6%) was similar to the national average (9.6%-13%),^{30,31} and at the cost of generalizability, this ethnically homogeneous population may minimize a confounding effect of ethnicity and socioeconomic status (and related risk factors). Ascertainment of HZ was based on physician diagnosis and predetermined retrospective criteria. Similarly, although our criteria for asthma have been used extensively in previous epidemiologic and laboratory studies, it should be subject to nondifferential misclassification with regard to outcome event (ie, incidence of HZ).

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

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