Asthma as a risk factor for zoster in adults: A population-based case-control study

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Background: We recently reported an increased risk of herpes zoster (shingles or zoster) in children with asthma, but little is known about whether the same is true for adults with asthma.
Objective: We determined whether asthma is associated with an increased risk of zoster in adults.
Methods: This study was designed as a population-based case-control study. Zoster cases during the study period were identified among adults (aged ≥50 years) who resided in Olmsted County, Minnesota. We compared the frequency of asthma between zoster cases and birthday- and sex-matched control subjects (1:2 matching) without a history of zoster. Asthma status was ascertained based on predetermined criteria. A conditional logistic regression model was used to assess the association of asthma with risk of zoster.
Results: A total of 371 zoster cases and their 742 matched control subjects were enrolled. Of the 371 cases, 246 (66%) were female, 348 (94%) were white, and the mean ± SD age was 66.8 ± 10.7 years. Twenty-three percent (n = 87) of zoster cases had a history of asthma compared with 15% (n = 114) of control subjects. Controlling for pertinent covariates and confounders, there was a significant association between a history of asthma and risk of zoster (adjusted odds ratio, 1.70; 95% CI, 1.20-2.42; $P = .003$). The population attributable risk percentage for asthma was about 10%.
Conclusions: Asthma is an unrecognized risk factor for zoster in adults. Consideration should be given to immunizing adults with asthma aged more than 50 years as a target group. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Asthma, herpes zoster, risk, adults, epidemiology*

Herpes zoster (zoster or shingles) is estimated to occur in up to 30% of all adults by age 80 years, with nearly 1 million cases a year in the United States.[1,2] The decade of life with the largest number of cases is 50 to 59 years, causing significant loss of work and productivity.[1] Yawn et al[1] reported an increasing trend of the incidence of zoster in Olmsted County, Minnesota, over time (3.2 to 4.1 per 1000 person-years between 1996 and 2001).[3] A prior study completed in Olmsted County using comparable data sources and definitions reported an incidence rate of 1.3 cases per 1000 person-years between 1945 and 1959, suggesting an increase of greater than 3-fold over the 56 years studied.[4] Although the reasons for this increase in zoster rates are unknown, the introduction of the childhood varicella vaccination (1995) is unlikely to account for the increasing trends of zoster in our study setting.

Despite the presumed immunosenescence with aging,[1,5,6] it is still unclear why some persons have zoster and others do not. Almost all (99.2% to 99.6%) of the US population aged 40 years or greater have serologic evidence for previous varicella infection and therefore are at risk for zoster,[5,7] but two thirds of persons will never have zoster.[1] Only 8% to 10% of patients with zoster have known significant immune suppression, potentially suggesting unrecognized risk factors.[1] In this respect little is known about the effect of conditions with immune dysfunction, such as asthma, on the risk of zoster.

Asthma represents one of the 5 most burdensome chronic diseases in the United States,[8] affecting 7% to 17% of the US population.[8-12] It increases the risk of serious and common microbial infections,[13-19] which might in part be accounted for by suboptimal innate and adaptive immune functions.[20-24] Thus we recently examined the relationship between asthma and the risk of zoster and found a significantly increased risk of zoster among children with asthma (adjusted odds ratio [OR], 2.07; 95% CI, 1.24-3.52).[25]

This population-based study expands our exploration further to assess whether asthma status is associated with the risk of zoster in adults. This study provides an important insight into the nature of the effect of asthma on the risk of infections because zoster is a unique non–airway-related latent viral activation in dorsal root ganglia, which is primarily controlled by cell-mediated immunity.[13,14,16,17]

METHODS

Study setting

Olmsted County, Minnesota, provides unique advantages for population-based epidemiologic studies because medical care is virtually self-contained within the community. In addition, when patients register with any health care

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Abbreviations used
ICS: Inhaled corticosteroid
OR: Odds ratio
REP: Rochester Epidemiology Project

providers in the community, they or their parents/legal guardians are asked to grant or refuse authorization of use of their medical records for research. Authorization is granted by more than 95% of all subjects.[26] Medical records research using the geographically defined population of Olmsted County was possible through the Rochester Epidemiology Project (REP), which has been continuously funded by the National Institutes of Health and maintained since 1960.[27-30] Within the REP,[31] each patient seen at any health care facility within the county has all diagnostic codes collected with health care services and site of service. This study protocol was approved by the institutional review boards at both Mayo Clinic and Olmsted County Medical Center.

Study design

The study was designed as a population-based case-control study, which compared the frequency of asthma before the index date among incident cases of zoster with that among birth date (±1 year)–, sex-, initial clinic or hospital registration date–, and index date (±1 year)–matched corresponding control subjects (1:2 individual matching) without a history of zoster. The index (incident) date for cases was the date of the first zoster diagnosis, and that for control subjects was the closest clinic visit date (within 1 year) to the index date of corresponding cases.

Case ascertainment

All potential zoster cases (≥50 years of age) occurring between January 1, 2010, and October 31, 2011, were identified from medical records by using a case ascertainment algorithm used for our previous study.[1,32] All potential zoster incident cases were identified from a broad search of diagnostic codes (International Classification of Diseases, Ninth Revision, codes 053.xx) for zoster and zoster complications. Medical records regarding each potential incident case were reviewed to verify that the case was indeed a new case of zoster based on the criteria for zoster. Confirmation required either (1) positive laboratory data supported with a Tzanck smear, viral culture, or a positive PCR test for zoster virus or the following (2) clinical criteria used in our previous study: (A) a statement of characteristic rash (vesicular rash on dermatome) in medical records, (B) signs or a statement of pain or itching at the rash site during the interview, and (C) a physician's diagnosis of zoster in the medical record. Exclusion criteria included (1) subjects without research authorization; (2) non-Olmsted County, Minnesota, residents; (3) another diagnosis explaining the rash, such as culture positive for herpes simplex; and (4) clinical conditions making ascertainment of asthma difficult, as listed in Table I.

Selection of control subjects

Two matched control subjects were randomly selected from the REP (ie, population-based sampling frame for Olmsted County, Minnesota, residents). The literature showed that 99.2% to 99.6% of the US population aged 40 or more years has serologic evidence for previous varicella infection, which was quite steady over time (1988-2004).[5,7] We did not assess serologic evidence for a history of varicella infection in the past for control subjects.

Determination of exposure status (asthma status)

We applied predetermined criteria for asthma delineated in Table I, which have been extensively used in research for asthma epidemiology and have shown excellent construct validity and reliability (0.72-0.92).[13,14,17,18,33,34] Because most subjects with probable asthma (85%) had definite asthma over time, we combined both probable and definite asthma.[33]

Other variables

We collected pertinent variables for this study: asthma medication and control status, comorbid conditions at the time of the index date, other atopic conditions before the index date, zoster vaccination before the index date, and proxy measures for health care access (influenza vaccination in a preceding year and pneumococcal polysaccharide vaccination). The comorbid conditions examined in this study are listed in Table II. Other atopic conditions were ascertained by a diagnosis of atopic dermatitis, allergic rhinitis, and food allergy documented in medical records before the index date of zoster. We collected data on corticosteroid therapies and asthma control status within 6 months of the index date of zoster. We defined poorly controlled asthma as any asthma symptoms documented in medical records, systemic corticosteroid therapy for asthma symptoms, unscheduled visits for asthma, visits to the emergency department for asthma, or hospitalization for asthma within 6 months before the index date.[35,36]

Data analysis

Matched analysis through conditional logistic regression was used, with zoster case status as the target end point in the model and asthma status as the primary explanatory variable. In each model the matching variables (age, sex, and years since registration) were included as adjusting covariates to control for any residual confounding not prevented by the matching. Asthma was carried forward into a multivariable model along with other factors screened from univariable modeling by using an α level of 0.2.[37] Atopic dermatitis, allergic rhinitis, and food allergy, which share similar immunologic characteristics with asthma, were left out of this model to avoid collinearity, although each was included in separate multivariable models (removing asthma) to test the association with zoster. We calculated the population attributable risk percentage of asthma for zoster.[38] We examined a differential effect of asthma on the risk of zoster among different age groups by assessing the statistical significance of the interaction term between asthma and age groups. Incidence of zoster was estimated among adults in the county during the 2-year study time frame, with rates adjusted for age and sex by means of direct standardization against the 2010 US population. All analyses were performed with SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS

Study subjects

Of the total 475 potential zoster cases identified during the study period, 93 subjects were excluded from incidence analyses for the following reasons: non-Olmsted County residents (n = 62), no research authorization (n = 19), and no physician's diagnosis of zoster in medical records during the study period (n = 12). For analyses pertaining to the relationship between asthma and zoster, an additional 10 subjects were excluded because of clinical conditions making asthma ascertainment difficult (2 for pulmonary fibrosis, 2 for bronchiectasis, 5 for significantly decreased pulmonary function defined by an FEV_1 <50% or diminished diffusion capacity, and 1 for significant scoliosis) and 1 because of insufficient medical records to determine asthma status.

Based on a total of 382 incident cases, the overall age- and sex-adjusted incidence rate of zoster during our study period was 4.3 (95% CI, 3.9-4.7) per 1000 person-years. The age-adjusted sex-specific incidence rates (per 1000 person-years) were 5.3 (95% CI, 4.7-6.0) in female subjects and 3.2 (95% CI, 2.7-3.8) in male subjects. The sex-adjusted age-specific incidence rates were 3.1 (95% CI, 2.6-3.7) in subjects aged 50 to 59 years, 4.5 (95% CI,