Childhood atopic dermatitis and warts are associated with increased risk of infection: A US population-based study

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Background: Previous studies suggested that atopic dermatitis (AD) is associated with aberrant immune responses, which might predispose toward both cutaneous and extracutaneous infections. The goal of this study was to determine whether childhood AD is associated with increased risk of warts, extracutaneous infections, and other atopic diseases and how these disorders cosegregate.

Methods: The 2007 National Health Interview Survey from a nationally representative sample of 9417 children age 0 to 17 years was used.

Results: Children with AD and other atopic disease had higher odds of warts. In contrast, children with AD with or without other atopic disease had higher odds of extracutaneous infections, including strep throat, other sore throat, head or chest cold, influenza/pneumonia, sinus infections, recurrent ear infections, chickenpox, and urinary tract infections ($P < .0001$). Children with AD and other atopic disease had a higher number of infections than those with either disorder by itself ($P < .0001$). Warts were also associated with increased odds of all extracutaneous infections ($P < .0001$), except recurrent ear infections. Children with warts and AD had a higher number of infections than those with either disorder alone ($P < .0001$). Finally, children with AD and warts had higher odds of ever receiving a diagnosis of asthma, current asthma, asthma exacerbation in the past year, hay fever, and food allergy. Children with AD with warts had even higher odds of asthma, hay fever, and food allergies than those with AD and no warts.

Conclusions: The associations between childhood AD, atopic disease, warts, and extracutaneous infections suggest that barrier disruption, immune disruption, or both contribute to susceptibility to warts and extracutaneous infections in children.

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Key words: *Atopic dermatitis, eczema, asthma, allergic disease-rhinoconjunctivitis, hay fever, food allergies, respiratory allergies, warts, verruca vulgaris, age, race, ethnicity, Hispanic, infections, strep throat, influenza, head cold, pneumonia, sinusitis, ear infection, urinary tract infection*

Abbreviations used
AD: Atopic dermatitis
aOR: Adjusted odds ratio
HPV: Human papilloma virus

Susceptibility to cutaneous infections, such as *Staphylococcus aureus* and warts (cutaneous infection with human papilloma virus [HPV]), has been linked to atopic dermatitis (AD), and a tendency toward skin infection is one of the minor criteria of Hanifin and Rajka.[1] It is well established that barrier disruption related to AD is associated with increased cutaneous viral infections, including eczema herpeticum and molluscum contagiosum.[2-5] However, there are conflicting reports about the risk for acquisition of warts in patients with AD. Several well-designed international studies have challenged this dogma with reports of lower prevalence of warts in children with AD.[6,7]

Recent studies demonstrated aberrant Toll-like receptor signaling and innate immunity in patients with AD[8,9]; increased thymic stromal lymphopoietin,[10,11] T_H2 and T_H22 cytokine,[12] and serum IgE levels and sensitization to cutaneous exposure to allergens[13]; and increased expression of FcεRI on Langerhans cells.[14] Silverberg and Simpson[15] recently found that childhood AD is associated with recurrent ear infections and multiple dental health comorbidities. This suggests that children with AD might be at higher risk for both cutaneous and extracutaneous infections.

Finally, little is known about how warts caused by HPV infection cosegregate with other infections. HPV is ubiquitous and commonly found on the skin of healthy children and adults without any history of warts.[16-18]

We hypothesized that there are specific subsets of patients with AD with increased risk for warts and extracutaneous infections. We hypothesize that certain host factors, such as impaired barrier or immune responses, contribute to susceptibility to warts. Thus children infected with warts might also be at greater risk for extracutaneous infections. We aim to study these associations in a representative cohort of the US population.

METHODS

National Health Interview Survey

This study was approved by the institutional review board at St Luke's–Roosevelt Hospital Center in New York City. We used the 2007 National Health Interview Survey (NHIS), which is collected by the National Center for Health Statistics and is the principal source of information on the health of the civilian noninstitutionalized population of the United States. A waiver of informed consent was obtained by the National Center for Health Statistics because the survey posed minimal risk and respondents were not identifiable by the recorded data. The survey included a separate questionnaire about children's health based on parental response to estimate the prevalence of various child health issues, including physical, emotional, and behavioral factors. The survey was administered in person to selected households by the Bureau of the Census using approximately 400 trained interviewers with

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computer-assisted personal interviewing. Subsequently, one child was randomly selected for the sample-child questionnaire. Interviews were conducted in English and Spanish. Using data from the US Bureau of the Census, weights were adjusted for age, sex, race, ethnicity, household size, and educational attainment of the most educated household member to provide a data set that was more representative of each state's population of noninstitutionalized children less than 18 years of age. All prevalence estimates presented reflect this complex weighting.

History of atopic disease and infectious comorbidities

AD was determined by asking the following question: "During the past 12 months, have you been told by a doctor or other health professional that (child) had eczema or any kind of skin allergy?" History of ever receiving a diagnosis of asthma was determined by asking the following question: "Has a doctor or other health professional ever told you that (child) had asthma?" Current history of asthma was determined by asking the following question: "Does (child) still have asthma?" One-year history of asthma exacerbations was determined by asking the following question: "During the past 12 months, has (child) had an episode of asthma or an asthma attack?" Hay fever was determined by asking the following question: "During the past 12 months, have you been told by a doctor or other health professional that (child) had hay fever or any kind of respiratory allergy?" Food allergy was determined by asking the following question: "During the past 12 months, have you been told by a doctor or other health professional that (child) had any kind of food or digestive allergy?" A composite binary variable was created for atopic diseases by using responses to the above 4 questions.

History of warts was determined by using the following NHIS question: "During the past 12 months, has (child) had warts?" History of episodes of other infections was determined by asking the following question: "During the past 12 months, has a doctor or other health professional told you that (child) had..." "strep throat or tonsillitis?," "sore throat other than strep or tonsillitis?," "influenza or pneumonia?," "sinusitis?," "three or more ear infections?," and "urinary tract infections?" History of an episode of chickenpox was determined by asking the following question: "Has (child) ever had chickenpox?" History of colds was determined by asking the following question: "Did (child) have a head cold or chest cold during those two weeks (of missed school days from illness)?"

Data processing and statistical methods

All data processing and statistical analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC). Bivariate and multivariate analyses of survey responses were performed with SURVEY procedures. Bivariate associations were tested by using Rao-Scott χ^2 tests. Significant predictors from bivariate analyses were included as covariates in multivariate logistic regression models. Adjusted odds ratios (aORs) and 95% CIs were determined. Complete data analysis was performed (ie, subjects with missing data were excluded). Our *a priori* hypothesis was that children with AD and other atopic disease might have more infections than those with AD alone. Therefore models were constructed that tested interaction terms between AD and other atopic disease. Similarly, models were constructed that tested interaction terms between AD and warts. Two- and 3-way interaction terms between other covariates were also tested. Interactions were only included in final models in cases of P values of less than .01 and modification of estimates by greater than 20%. In models of binary outcomes with significant statistical interactions, we constructed generalized linear models using a logit link function in PROC GLIMMIX. Similarly, in models of continuous outcomes, we constructed generalized linear models using a normal link function. *Post hoc* analyses were conducted of differences among the levels of one factor at a fixed level of the other factor. Least-squares means and aORs (95% CIs) were estimated for each combination of factors included in the interaction effects. The best model was selected by using the Bayesian information criterion, which penalizes for extra parameters and takes into account the large sample size.

Correction for multiple tests (k = 59) was performed by using the Bonferroni method and yielded a critical P value of .0008.

RESULTS

Population characteristics

Data were collected on a total of 9417 children. Overall, the prevalence of AD was 8.9% (95% CI, 8.2% to 9.6%) in US children. The prevalence of AD was significantly associated with age, African American race, non-Hispanic origin, higher household income and level of education, health care interaction in the past year, health insurance coverage, and birthplace in the United States (Table I).

Nine infectious causes were assessed, including warts (percentage prevalence, 3.3%; 95% CI, 2.8% to 3.8%), strep throat (percentage prevalence, 12.0%; 95% CI, 11.2% to 12.9%), other sore throat (percentage prevalence, 32.2%; 95% CI, 31.0% to 33.4%), head or chest cold (percentage prevalence, 14.1%; 95% CI, 13.2% to 15.0%), influenza/pneumonia (percentage prevalence, 6.4%; 95% CI, 5.7% to 7.0%), sinus infections (percentage prevalence, 7.2%; 95% CI, 6.6% to 7.9%), recurrent ear infections (percentage prevalence, 5.1%; 95% CI, 4.5% to 5.6%), chickenpox (percentage prevalence, 28.3%; 95% CI, 27.1% to 29.5%), and urinary tract infection (percentage prevalence, 1.4%; 95% CI, 1.1% to 1.6%). Of the subjects, 62.8% (95% CI, 61.6% to 64.0%) reported 1 or more of these 9 disorders. History of 1 or more infections was associated with older age, race, non-Hispanic origin, higher household income and level of education, family structure, and health care interaction in the past year (Table I). All significant associations from the bivariate analyses were considered potential confounding variables and included in multivariate models.

Association between AD and infections

There were significant interactions between AD and other atopic disease as predictors of infections (logistic regression, $P < .01$). Therefore generalized linear models with binary distributions were constructed, which tested pairwise differences of rows from the coefficient matrix. This approach allowed comparison of the effects of AD with or without other atopic disease with not having AD for each infectious outcome (Table II).

AD with or without other atopic disease was associated with higher odds of strep throat (aOR, 1.47 [95% CI, 1.46-1.47] and 1.56 [95% CI, 1.54-1.57]), other sore throat (aOR, 1.61 [95% CI, 1.61-1.62] and 1.91 [95% CI, 1.91-1.92]), head or chest cold (aOR, 1.47 [95% CI, 1.46-1.47] and 1.48 [95% CI, 1.47-1.48]), influenza/pneumonia (1.24 [95% CI, 1.23-1.24] and 1.67 [95% CI, 1.66-1.67]), sinus infections (2.18 [95% CI, 2.18-2.19] and 2.59 [95% CI, 2.58-2.60]), recurrent ear infections (1.41 [95% CI, 1.40-1.42] and 1.33 [95% CI, 1.32-1.34]), chickenpox (1.33 [95% CI, 1.32-1.33] and 1.19 [95% CI, 1.19-1.20]), and urinary tract infections (1.72 [95% CI, 1.70-1.73] and 3.12 [95% CI, 3.10-3.14]; Table II).

AD without other atopic disease was associated with a slightly lower odds of warts compared with no AD (0.91 [95% CI, 0.90-0.92]). In contrast, AD with other atopic disease was associated with higher odds of warts (1.83 [95% CI, 1.82-1.84]). We constructed additional logistic regression models to determine whether the increased odds of warts was due to atopic disease in general. Children who had atopic disease without AD had higher odds of warts (1.44 [95% CI, 1.43-1.44]), whereas children with atopic disease and AD had even higher odds (2.81 [95% CI, 2.79-2.84]).