Asthma

PATHOPHYSIOLOGY

Wheezeing Rhinovirus Illnesses in Early Life Predict Asthma Development in High-Risk Children


PURPOSE OF THE STUDY. Childhood asthma is often preceded by episodes of viral wheezing. Whether specific viral infections confer more risk for future development of asthma is incompletely understood. Associations between the timing and cause of early viral infections and the subsequent risk of childhood asthma were assessed in a cohort of children at high risk.

STUDY POPULATION. A total of 259 children were monitored prospectively from birth to 6 years of age in the Childhood Origins of Asthma (COAST) study. To qualify for the COAST study, ≥1 parent was required to have respiratory allergies (defined as ≥1 positive aeroallergen skin tests) and/or a history of physician-diagnosed asthma.

METHODS. The etiology and timing of specific viral wheezing respiratory illnesses during early childhood were assessed by using nasal lavage, culture, and multiplex reverse transcriptase-polymerase chain reaction assays. The relationships of these virus-specific wheezing illnesses and other risk factors to the development of asthma were analyzed.

RESULTS. A specific viral etiology was identified in 90% of wheezing illnesses. Wheezing with respiratory syncytial virus (RSV) (odds ratio [OR]: 2.6), rhinovirus (RV) (OR: 9.8), or both RV and RSV (OR: 10) from birth to age 3 years was associated with increased asthma risk at age 6 years. In year 1, both RV wheezing (OR: 2.8) and aeroallergen sensitization (OR: 3.6) independently increased asthma risk at age 6 years. By age 3 years, wheezing with RV (OR: 25.6) was more strongly associated with asthma at age 6 years than was aeroallergen sensitization (OR: 3.4). Nearly 90% of children with wheezing with RV at age 3 subsequently developed asthma, regardless of the presence or absence of aeroallergen sensitization.

CONCLUSIONS. In children at high genetic risk, early childhood wheezing in the outpatient setting caused by RV infection is a strong risk factor for the development of asthma at age 6 years.

REVIEWER COMMENTS. We have been familiar with the previous studies focused on associations of early RSV infections and the subsequent risk for asthma. Persistent wheezing associated with early-onset RV infection seems to be a better indicator of asthma risk than RSV infection. It will be interesting to follow the COAST study results as they monitor these children throughout childhood and beyond. A still-unanswered question is: do early viral infections cause asthma or just unmask predisposed asthma?

Evidence of a Causal Role of Winter Virus Infection During Infancy in Early Childhood Asthma


PURPOSE OF THE STUDY. In the first year of life, ∼20% of children have ≥1 episode of respiratory illness with wheezing. Other studies have shown that certain respiratory viruses confer an increased risk of developing later childhood asthma. Whether these common respiratory viruses cause asthma or are a marker of individuals predisposed to developing asthma is unknown. The timing of birth in relation to the winter virus peak and whether this alters the risk of developing early childhood asthma are investigated in this study.

STUDY POPULATION. A population-based, birth cohort study of 95 310 children who were born between 1995 and 2000 and followed through 2005, who were continuously enrolled in the Tennessee Medicaid program from birth through early childhood, representing 25% of the annual births in Tennessee, was performed.

METHODS. The criteria for defining asthma variables and classification represent a minor flaw, because they were not defined a priori and were based on adult data. However, the authors used well-designed methods to make certain that the main outcome variables were defined in the best way the data allowed. Infant birth in relation to the winter virus peak was defined for each infant as the infant’s age in days from birth to the first winter virus peak. The annual winter virus peak was defined as the first day of the week with the highest number of bronchiolitis hospitalizations for that winter season.

RESULTS. During the 5 winter virus seasons, the risk of developing asthma tracked with the timing of infant birth in relation to the winter virus peak among the 95 310 children studied from birth through early childhood. Infant birth ∼4 months before the winter virus peak carried the highest risk, with a 29% increase in the odds of developing asthma, compared with birth 12 months before the peak (odds ratio: 1.29). Infant age at the winter virus peak was comparable to or greater than other known risk factors for asthma, such as maternal smoking or maternal asthma. Over the 5 study seasons,
the increase in the incidence of bronchiolitis during infancy paralleled the subsequent increase in the cumulative incidence of current high-risk asthma defined between 4 and 5.5 years of age and offset by 5 years from the birth season in the same cohort of children.

CONCLUSIONS. This study demonstrates that the timing of birth in relation to the winter virus season confers a differential and definable risk of developing early asthma, establishing winter virus seasonality as a causal factor in asthma development. The authors have demonstrated that increasing rates of infant bronchiolitis in the past 10 years parallel the 5-year–offset increases in asthma at 5 years of age among these children.

REVIEWER COMMENTS. Timing of birth in relation to the winter virus peak independently predicts asthma development, with the highest risk estimated to be birth at 121 days before the winter virus peak of any given year. This age confers a 29% increased risk of developing childhood asthma. These findings, taken with findings from the Childhood Origins of Asthma study (reviewed above), are exciting and will fuel the debate about interventions for avoiding viral infections in infancy (are they a credible target?). There is controversy in this area, because children who attend day care centers and who are more exposed to recurrent respiratory infections have been shown to have less asthma later in life. Possibly some subgroups at greater risk of developing asthma, such as infants who are young at the beginning of the virus season and those with an atopic background, may benefit most from preventive and therapeutic interventions.

Acute, But Not Resolved, Influenza A Infection Enhances Susceptibility to House Dust Mite-Induced Allergic Disease


PURPOSE OF THE STUDY. To examine the consequences of exposure to a low dose of the common aeroallergen house dust mite (HDM) during the course of an influenza A infection.

METHODS. The response to allergen exposure was evaluated at 3 distinct time points, relative to influenza infection. To evaluate responses to allergen exposure during the acute phase of infection, mice were inoculated intranasally with influenza type A virus and then exposed to a low dose of HDM daily for 10 days during the peak of acute inflammation. The second experiment investigated whether HDM-associated changes in the inflammatory response were transient or long-lasting. The third experiment evaluated HDM-associated inflammatory response.

RESULTS. In mice inoculated with influenza A, there was a preferential increase in the activation of CD8+ T cells over CD4+ T cells and an increase in antigen-presenting cells, particularly plasmacytoid dendritic cells, as expected after a viral infection. Exposure to a low dose of HDM during the acute phase of influenza infection led to significantly increased numbers of mononuclear cells and eosinophils in the lung. Flow cytometry revealed a robust increase in the number of CD4+ T cells, specifically T-helper 2 (Th2) cells, and this increase in Th2 cells was much stronger in the influenza-infected HDM group, compared with the HDM-alone group. Exposure to HDM during the acute phase of influenza infection also resulted in significantly elevated levels of HDM-specific immunoglobulin G1 (IgG1) and IgG2a. Mice exposed to HDM allergen during the acute infection also demonstrated enhanced lung dysfunction and significantly greater goblet cell metaplasia and mucus production, compared with mice treated with HDM allergen alone. Mice that were rechallenged with HDM (experiment 2) showed responses similar to those listed above. Finally, mice with a first exposure to HDM that occurred after resolution of the influenza infection had an attenuated HDM-associated inflammatory response.

CONCLUSIONS. The study shows that the Th1 immune environment created during the acute phase of influenza infection leads to enhanced, rather than attenuated, allergic sensitization and inflammation in response to aeroallergen exposure and that these effects are long-lasting. In contrast, allergen exposure that occurs after the resolution of influenza infection does not result in an enhanced inflammatory response.

REVIEWERS COMMENTS. There has been great interest in finding ways to divert the immune system away from a Th2 allergic profile. Previous studies suggested that viral infection may afford protection against allergic disease by promoting Th1 responses. This study clearly shows that, despite the Th1 state induced by influenza A infection, the immune system is driven to a robust response to concomitant allergen exposure. Whether influenza or other viruses play a similar role in humans remains to be seen.
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