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The spectrum of severe wheezing in childhood

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Key words: Wheezing, asthma, rhinovirus, respiratory syncytial virus, allergy

Viruses are closely associated with acute and chronic wheezing, and this is especially true in children. Studies involving outpatients¹ or children who present to emergency departments^{2,3} have identified virus- and host-specific factors that modify the risk of virus-induced wheezing. It is established that respiratory syncytial viruses (RSVs) cause most wheezing episodes in infancy, whereas rhinoviruses have been identified as major causes of acute exacerbations of asthma in children older than 2 years of age. A number of factors influence the risk of virus-induced wheezing in infancy, including genetics,^{4,5} reduced lung size,⁶ and exposure to tobacco smoke⁷ and other children.⁸ In older children allergy and viral infections synergistically promote wheezing.^{2,3}

In this issue of the Journal, Heymann et al⁹ extend our understanding of this subject with a well-designed study of viral infections, allergy, and wheezing in a large group of hospitalized children. This case-control study involved 113 children of all ages admitted to the hospital for wheezing, and an equal number of nonwheezing control children, including those who had respiratory illnesses but were not wheezing. Nasal lavage specimens were analyzed for respiratory viruses, and sera were analyzed for allergen-specific IgE. The findings of any case-control study are profoundly influenced by the selection of control subjects, and in this study the control group was matched in terms of age, sex, and, importantly, the month of admission, which has a strong influence on the incidence of specific viral infections. Moreover, the study was conducted over a 12-month period to encompass seasonal variability of viral epidemiology and included an exceptionally high rate of participation, with 93% of eligible subjects taking part.

The result of this study design helps to define in broad strokes the spectrum of children who have severe

Abbreviation used

RSV: Respiratory syncytial virus

wheezing illnesses. In infancy viral infections caused the wheezing illnesses, and allergies had little influence on this process. RSV in particular was isolated much more often from the wheezing group compared with the control group. As expected, the seasonality of this infection was sharply confined to the cold-weather months. Notable in this study is the high prevalence (46%) of illnesses in which more than one virus was detected. This finding is a testament to the sensitive viral diagnostics used in the study, underscores the ubiquitous exposure to viruses in this age group, and confirms previous reports indicating that infants with multiple viral infections tend to be quite ill.¹⁰

Remarkably, rhinoviruses were the main pathogens associated with wheezing in infancy at other times of the year. Rhinoviruses were more likely to be isolated from wheezing than control subjects, although the difference was not as dramatic as that observed for RSV, suggesting a substantial role for host-specific factors in determining wheezing with rhinoviruses. Why do some infants wheeze with rhinoviruses, which are generally associated with relatively mild illnesses? Are some strains of rhinovirus simply more virulent, or is rhinovirus-induced wheezing in infancy an indication of a problem with the host?

Although these clinically important questions have yet to be fully resolved, there is evidence that infants who wheeze with rhinovirus infections are indeed different in terms of risk factors, prognosis, and perhaps even response to treatment. For example, previous studies have indicated that immunologic factors, such as deficient type 1 or type 2 IFN responses, can lead to more frequent viral infection, more severe viral infection, or both.^{8,11-13} In addition, Kotaniemi-Syrjanen et al¹⁴ in Finland performed viral diagnostics on nasal secretions of infants who were hospitalized for a wheezing illness and then evaluated these children for allergies and asthma 6 to 7 years later. At the time of the initial visit, children who wheezed with rhinovirus infection were more likely to have atopic dermatitis. At the follow-up visit, those who had wheezed with rhinoviruses in infancy had a 4-fold increase in the risk of asthma compared with children who had wheezed with other viruses, principally RSV. Finally, there are

From the University of Wisconsin-Madison.

Supported by grants P01-HL070831, P01 AI50500-01, and NIAID-DAIT-02-11. Received for publication May 24, 2004; revised May 27, 2004; accepted for publication May 27, 2004.

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J Allergy Clin Immunol 2004;114:236-8.

0091-6749/\$30.00

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doi:10.1016/j.jaci.2004.05.059

preliminary indications that knowing which virus causes a wheezing episode in infancy could be an important guide to therapy. In an abstract presented at the most recent American Academy of Allergy, Asthma and Immunology meeting, Jartti et al¹⁵ reported that administration of oral prednisolone to wheezing infants in the hospital resulted in striking benefit for those infected with rhinoviruses and enteroviruses, but not for RSV-infected infants. Collectively, these studies indicate that host factors related to both the lung and immune system help to determine the severity of rhinovirus infections and the risk of wheezing. Moreover, the cause of virus-induced wheeze in infancy might be an important factor in determining response to therapy and long-term prognosis.

In the new data presented by Heymann et al,⁹ viral infections were also important causes of wheezing in the older children (≥ 3 years of age), but both the seasonality and pathogens were different. The peak of hospitalizations occurred in the fall, as has been observed in other studies, and rhinoviruses were most often detected. In this age group the authors confirmed their previous observations that allergic sensitization and viral infections are independent and synergistic risk factors for the development of wheezing^{2,3} and extend these observations to severe exacerbations leading to hospitalization. It appears, from studies conducted in adults, that sensitization and allergen exposure together are required for the synergistic effects of viral infections.¹⁰ Additional studies are needed to confirm this finding and to determine whether this is a consequence of allergen-induced inflammation, airway responsiveness, or some other factor.

Viruses were detected in 68% of hospitalized children aged 3 to 9 years and in 50% of those aged 10 to 18 years: this is lower than previous recovery rate estimates of 80% to 85% in outpatient studies.^{1,2} Remarkably, the seasonal distribution of wheezing in the virus-positive and virus-negative children were nearly identical: the October peak of hospitalizations in both groups closely corresponds with a return to school and the consequent common cold season.¹⁶ This seasonal coincidence suggests that some of the “virus-negative” episodes were in fact caused by viral infections. There are several potential barriers to optimal viral detection, even with the sensitive viral diagnostics used in this study. First, previous studies have found that the peak of viral shedding in nasal secretions is during the early stages of infection. Children hospitalized for wheezing, which typically lags behind the onset of cold symptoms by a couple of days, are likely to be past the optimal time for viral diagnostics. Second, several new respiratory viruses have been discovered since this trial was conducted, including metapneumovirus¹⁷ and new coronaviruses.^{18,19} Finally, there are a large number of rhinovirus serotypes: after a decade or so of cataloguing new isolates, virologists quit counting at just over 100. Although current PCR technology is much more sensitive than viral culture for diagnosing rhinovirus infections, it is unlikely that any single set of primers can detect all of the known serotypes, let alone those that have yet to be discovered.

Despite these limitations in determining the precise number of infected children, there is little doubt that with increasing age the rate of viral isolations gradually diminished, the prevalence of allergic sensitization increased, and a greater number of exacerbations occurred independently of viral infection. What caused the severe acute wheezing episodes in the children with no detectable viruses? The authors suggest that allergen exposure is a likely culprit. Dust mite allergy was most closely associated with the risk of wheezing, and in fact, there are data from the same medical center demonstrating that levels of dust mite protein, although a perennial allergen, vary somewhat with the season and are maximal in late summer and early fall. *Alternaria* species is an important aeroallergen during this time period, and *Alternaria* species allergy is not only a risk factor for persistent childhood asthma but is also associated with acute, severe exacerbations.²⁰ Another factor to be considered is pollution, and it is likely that the indoor environment, particularly the presence of tobacco smoke, is most important in a relatively small city, such as Charlottesville. Among the wheezing infants, there was a trend toward increased exposure to maternal smoking.

The comprehensive nature of this well-designed study in relation to season, age groups, and viral pathogens detected has helped to clarify the relationships between viruses and wheezing illnesses in childhood. Although this is a cross-sectional study with a limited ability to predict the natural history of viral and wheezing illnesses, when considered together with a multitude of other clinical studies, a coherent story begins to emerge. Wheezing in infancy is predominantly viral, and risk factors include those related to the lung, the immune system, and the environment. Allergy assumes a progressively greater role, and in some cases the primary role for severe exacerbations during the second decade of life. Beyond the documentation of individual risk factors, these results further develop the theme that an isolated viral respiratory infection or exposure to an airborne allergen or pollutant is rather unlikely to precipitate a hospitalization caused by asthma. Combinations of noxious stimuli, each of which is likely to exert its effects through distinct mechanisms and pathways, might generally be required to produce severe episodes of wheezing and airway obstruction.^{2,3,10,21} This model has important implications regarding treatment. Although for the foreseeable future it might be difficult to reduce the prevalence of common viral infections, such as rhinoviruses and RSV, many of the other risk factors, including environmental exposures and allergic airway inflammation, might be amenable to change or at least preventive treatment.

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