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POINT OF VIEW

The connection between early life wheezing and subsequent asthma: The viral march

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Abstract

Several new lines of evidence suggest that alterations in immune responses which predispose to bronchial obstruction during acute respiratory infection, especially with rhinoviruses, may explain to a considerable extent the link between early life wheezing and subsequent asthma; above all among those schoolchildren who are prone to having recurrent asthma exacerbations. The nature of these alterations is currently the subject of considerable scrutiny, but cross-sectional studies suggest that deficits in innate immune responses mediated by interferon type I and III are present in lung macrophages and epithelial cells of adult asthmatics. Similarly, long-term follow-up studies suggest that deficits in interferon gamma responses in the first year of life predispose to recurrent episodes of wheezing from the preschool years and into early adolescence. A better understanding of the “viral march” could yield new therapeutic approaches for the prevention and treatment of acute severe airway obstruction during childhood.

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Several longitudinal studies have provided convincing evidence that, in most cases of asthma, the first symptoms of the disease occur during the preschool years.^{1–3} Young children who will go on to develop asthma later in life usually have recurrent episodes of wheezing, cough, and difficulty to breathe (“persistent wheezers”),⁴ and these episodes are associated with molecular evidence of viral respiratory infection in up to 90% of cases.⁵ However, the majority of infants aged <1 year who wheeze remit by the age of 3 (the so-called transient wheezers⁶), and their episodes are also associated with viral infections. Until very recently, a predisposition to allergy was the main disease

mechanisms believed to connect early life wheezing with subsequent asthma.⁷ The purpose of this brief comment is to review the evidence which suggests that susceptibility to infection with rhinovirus may be a critical additional factor explaining this connection.

The atopic link

Our group in Tucson was among the first to show that increased immune responses of the type that characterize the allergic phenotype were present at the time of the first lower respiratory illness (LRI) in children who would later go on to develop persistent wheezing. We showed that

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persistent wheezers had significantly higher total serum IgE levels during the acute phase of the LRI as compared with convalescence, whereas no change in total serum IgE was observed in transient wheezers.⁸ We also observed that, whereas in transient wheezers there was the expected, acute eosinophilic response to viral infection, no such response was observed in persistent wheezers.⁸ We concluded that a predisposition to T-helper type-2 (Th-2) responses was an important determinant of asthma risk which could be already detected at the time of the first LRI. However, we were unable to demonstrate in these studies that it was a Th-2-type response to the virus itself which determined the involvement of the lower airways in persistent wheezers and that some alternative mechanism explained acute airway obstruction of transient wheezers. This idea had been proposed years earlier by Welliver et al,⁹ who suggested that, at the time of the acute early life infection, specific IgE antibodies against respiratory syncytial virus (RSV) were more likely to be produced by persistent wheezers than by transient wheezers. Experimental models have suggested that this mechanism may indeed play a role in the development of bronchial hyperresponsiveness in mice,¹⁰ but the involvement of antiviral IgE in human asthma has not been clearly established. Sly et al recently reviewed the convincing evidence suggesting that markers of an atopic predisposition can be detected very early in life in persistent wheezers, indicating that such predisposition is a major risk factor for the development of asthma in early wheezers.¹¹

The viral link

The availability of a new, molecular diagnostic method for the detection of viral infections has opened a new phase in our understanding of the roots of asthma in early life. In 2003, Kotaniemi-Syrjanen¹² et al. first attempted identification of rhinoviruses in samples obtained from children with or without subsequent asthma who were hospitalised for acute wheezing episodes in infancy. They found that the odds of identifying rhinoviruses (as compared to any other virus or no virus) in samples obtained during those acute episodes were 4 times higher in children who had asthma than in those who did not have asthma at age 6–7 years. In a subsequent longitudinal study, Jackson and coworkers⁵ observed that, among children at high risk for asthma and allergies, those who had confirmed rhinovirus LRI during the first 3 years of life were up to 10 times more likely to have asthma in the early school years than those who had no LRI. Of interest, they also reported that children who had LRI due to RSV were 4 times more likely to have asthma at age 6 than those who did not have LRIs. This confirmed our own findings in a population sample of unselected children, in which we also showed that the association between RSV and subsequent wheezing decreased steadily after age 6 and was non-significant by age 13¹³. Kusel et al¹⁴ observed that asthma at age 5 years was 4 times more likely to occur in children who had wheezy illnesses due to rhinovirus or to RSV in early life than in those who had no LRIs, and this association was mainly observed among children who became sensitised to allergens before age 2.

It is of great interest that, in the decade prior to these observations, several cross-sectional and longitudinal studies had shown that, in older children and adults, evidence of rhinovirus infection can be found in 50–75% of all acute asthma exacerbations.^{15,16} Moreover, long-term follow-up studies such as the Childhood Asthma Management Program¹⁷ clearly established that childhood asthma is a heterogeneous condition, with up to two-thirds of patients having acute exacerbations requiring oral corticosteroid therapy, with the remainder not presenting with any such more severe episodes during 4–6 years of follow-up. These studies indicated that there could be a group of children who are indeed predisposed to having abnormal responses to viruses, and acute, severe episodes of airway obstruction could be the expression of this susceptibility.¹⁸ In support of this contention, *in vitro* studies have suggested that both bronchial epithelial cells and macrophages obtained from persons with asthma and stimulated with rhinoviruses have deficient production of interferon beta¹⁹ (a type I interferon) and interferon lambda²⁰ (a type III interferon) as compared with cells obtained from non-asthmatic subjects.

It is thus plausible to postulate that one potential link between early viral wheezing and subsequent asthma could be a congenital (or very early acquired) susceptibility to infection with rhinoviruses. Unfortunately, no studies have assessed type I or type III interferon responses in young children with or without wheezing and therefore, it is not possible to establish if a deficit in responses mediated by these interferons connects early life wheezing with subsequent asthma. However, there is indirect evidence that deficits in immune responses may be present early in life which predispose to subsequent recurrent episodes of airway obstruction up to the adolescent years. We recently reported²¹ that, in the Tucson Children's Respiratory Study, the risk of having acute episodes of wheezing between 2 and 13 years was inversely related to interferon-gamma responses by mitogen-stimulated peripheral blood mononuclear cells at a mean age of 9 months (*p* value for linear association=0.002). Of interest, these results were independent of any evidence of allergic sensitisation occurring during the follow-up period. Unfortunately, we were unable to determine from these studies if the observed deficits in interferon-gamma were responsible for the long-term susceptibility to acute wheezing episodes or if otherwise they were a marker of a more generalised alteration in immune responses. Moreover, we could not assess incidence of rhinovirus infection in these young children with the diagnostic tools available in the 1980s and thus, could not determine if the observed deficits predisposed specifically to such infections. Nevertheless, our results do suggest that further studies of the potential role of genetic and developmental factors that could predispose to abnormal responses to respiratory viruses could shed considerable light on the pathogenesis of childhood asthma.

Conclusions

There is considerable new evidence suggesting that the march from early life wheezing into adult asthma stands on

two legs: atopy and viral infection.²² Data from longitudinal studies²³ indicate that chronic exposure to aeroallergens in subjects with early sensitisation to such allergens plays a role in the transition from recurrent episodes of airway obstruction, which is characteristic of children asthma-like symptoms in early life, to persistent hyperresponsiveness, deficits in lung function and weekly or even daily respiratory symptoms as is usually observed in older children and adults with asthma. However, a significant proportion of school-children and adults with asthma show abnormal acute responses to rhinoviruses, and careful follow-up studies suggest that these abnormal responses were already present in these same subjects when they were infants or young children. The most parsimonious explanation for this association is that abnormalities in immune responses that are first expressed in the toddler persist into the school years creating a continuum of susceptibility. Since acute wheezing in early childhood and asthma exacerbations in older children and adults account for a very high proportion of the morbidity and health care cost associated with asthma and related disorders,²⁴ elucidating the genetic and molecular mechanisms which determine this continuum could provide us with potent new tools for the prevention and treatment of these disorders.

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