

Respiratory Viral Infections and Early Asthma in Childhood

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ABSTRACT

Respiratory viral infections profoundly influence the disease activity of wheezing illnesses and asthma in early childhood. Viral bronchiolitis shares many features with asthma and a subset of children develop recurrent wheezing after their initial illness. Recently mechanisms for virus-induced exacerbations of childhood asthma are beginning to be focused on and defined. Viruses cause systemic immune activation and also produce local inflammation. These factors are likely to affect airway pathogenesis leading to airway narrowing, an increase in mucus production, and eventually bronchospasm, and airway obstruction. These new insights related to the pathogenesis and disease activity are likely to provide new targets for the therapy and prevention of early asthma in childhood.

KEY WORDS

allergy, asthma, childhood, respiratory viral infection

INTRODUCTION

Respiratory viral infections and asthma are closely related in all age of childhood. All infants experience acute infections, but less than half develop wheezing with these illnesses. Of these children, most have a full recovery, but a subset of viral infections may play a role in the inception and exacerbation of asthma in childhood.^{1,2} On the other hand, hygiene hypothesis suggested that children who have grown up with contact with other children at home or in day care appear to have a reduced risk for allergies and asthma, which some types of infections early in life stimulate the T helper 1 (TH1) type of the immune system.³ Nevertheless, it is clear that respiratory viral infection remain an important cause of acute wheezing in infancy and early childhood, and accounts for half or more acute visits and hospitalizations for asthma. Several distinct wheezing phenotypes have been described in childhood by Martinez *et al.* (Fig. 1).⁴ First, infants who wheeze primarily with respiratory infections, the so-called transient early wheezers, share many features with asthma, and this may constitute a distinct subtype of asthma. This type is characterized by episodic small airway obstruction, plugging of the airway with shed epithelial cells and excess mucus, and recurrent bronchial obstruction and

wheezing. Although virus-induced wheezing is common in infants, it is important in this age to consider other causes for recurrent wheezing due to factors unrelated to the small airways, such as congenital heart disorders, anatomical abnormalities of the airways, and primary immunodeficiency. Without these conditions, recurrent episodic wheezing in infancy and early childhood is almost caused by acute viral infections, and recognition of this relationship in the natural history of childhood asthma has led to speculation that viral infections may play an important role to cause asthma. Secondly, some older children continue to wheeze with viruses, and very little else, and this condition has been described as non-atopic wheezer, which seems to remit in adolescence, although there may be a small subset of adults with a similar pattern. Finally, typical IgE associated atopic asthma in childhood often begins with virus-induced wheezing in infancy, but can also start later on in childhood in association with allergic sensitization. Infants with recurrent wheezing and other atopic features, such as atopic dermatitis, or a family history such as parent or siblings of allergic disorders are at most important risk factor to go on to develop atopic asthma in older childhood or adolescents.⁵ Affected children can have daily symptoms, and these can be cemented by seasonal or perennial exposure to aller-

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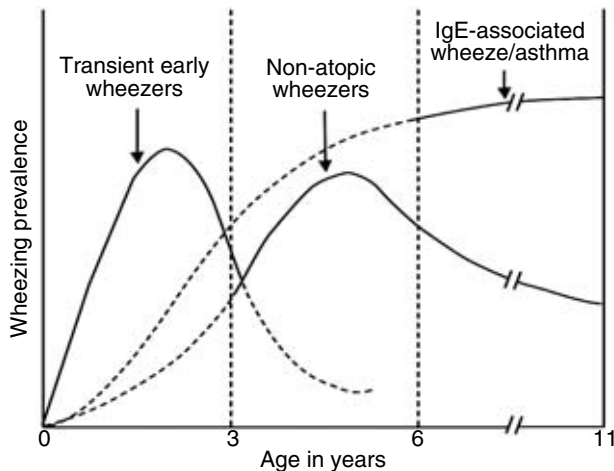


Fig. 1 Adapted from Martinez FD. *Pediatr. Infect. Dis. J.* 2003; 22: S76-S82. Asthma phenotypes: wheezing phenotypes in children. Hypothetical yearly peak prevalence of wheezing for the three different wheezing phenotypes in children. Prevalence for each age interval should be the sum of the areas under each curve. This classification of wheezing phenotypes should not imply that groups are exclusive. *Dashed lines* suggest that wheezing can present different curve shapes many factors, including overlap of groups.

gens.

These subtypes of asthma have unique risk factors and clinical features, providing strong evidence that the pathophysiology of each disorder is distinct. One critical factor is age, and each period of childhood is associated with a different mixture and prevalence of wheezing disorders. It is reasonable to think of wheezing disorders that immunologic development, allergic sensitization, and asthma phenotypes are continuous with changes in lung physiology from infancy to older childhood.⁶

THE CAUSING VIRUS INFECTIONS OF WHEEZING IN EARLY CHILDHOOD

The specific pathogens that most often cause infantile wheezing are respiratory syncytial virus (RSV), rhinoviruses (RV), parainfluenza viruses (PIV), metapneumovirus, and influenza viruses.^{7,8} RSV is the major cause of bronchiolitis during the late fall and winter and this virus accounts for about 70% of these episodes.⁹ Bronchiolitis, however, represents only the most severe pattern of infections since most children are infected with this virus by age 2 years.¹⁰ These aged children are most prone to develop lower respiratory tract symptoms, suggesting that a developmental component is an important cofactor in determining the severity of illness.¹¹ Another virus associated with bronchiolitis in these ages is the metapneumovirus, which causes approximately 10–15% of the non-RSV

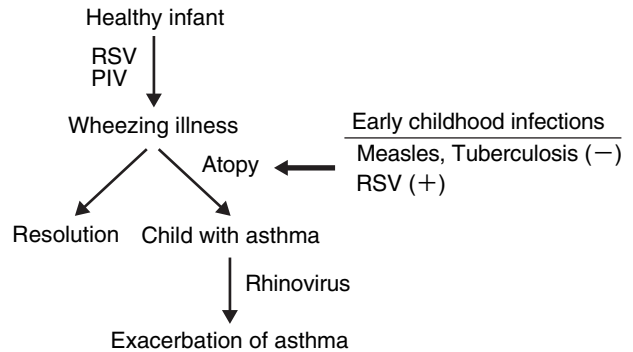


Fig. 2 Relationship of viral infections to acute wheezing illnesses and asthma. RSV: respiratory syncytial virus; PIV: parainfluenza virus. (–) expresses inhibition, (+) expresses stimulation.

wheezing illness during the bronchiolitis season.¹² These viruses have a natural history that is similar to RSV. Influenza viruses are the other major winter virus, and the severity of symptoms is strongly dependent on the prevalent serotype. Infants are clearly at greater risk of developing more severe illnesses, including lower respiratory infection with wheezing. PIV infections also account for a significant percentage of wheezing illness in infants throughout the year.

Rhinoviruses are now recognized as an important cause of wheezing in infancy and childhood. Although the growth of most RV is impaired at temperatures found in the alveoli, temperatures in over medium-sized airways are ideal for the growth of RV (Fig. 2).¹³

Premorbid measurements of lung function indicate that children with reduced levels of lung function in infancy are at increased risk of chronic lower respiratory tract injury following respiratory viral infections.¹⁴ Airway hyperresponsiveness measured in early infancy, more importantly, is also a risk factor for asthma later on in childhood.¹⁵

EFFECTS OF VIRAL INFECTIONS ON LUNG DEVELOPMENT IN CHILDHOOD

Viral infections can induce the synthesis of many of the factors that regulate airway and alveolar development and remodeling of airways.^{16–18} The possibility that acute inflammatory responses, together with efforts to repair virus-induced damage to lung tissue, could have long-term consequences on lung function has been evaluated in some animal study. The results from these studies strongly support the concept that viral infections that occur in a genetically susceptible host at a critical developmental time period could promote the inception of asthma.^{19,20}

Infancy is characterized by pulmonary alveolar multiplication and extensive remodeling of the air-

ways to accommodate growth and is also a period of increased susceptibility to viral infections. This coincidence, together with the observation that children with asthma can have structural lung changes and functional deficit at an early age, suggests that viral infections could adversely affect lung development.

VIRUS-INDUCED INFLAMMATORY MECHANISMS

The immune response to the virus can contribute to the pathogenesis of respiratory symptoms. For viruses such as RV, which infect relatively few cells in the airway, this may be the primary mechanism for airway symptoms and lower airway dysfunction.²¹ Virus-induced epithelial damage can also increase the permeability of the mucosal layer, facilitating allergen exposure to the immune cells, and exposing neural elements to promote neurogenic inflammation.^{22,23} In addition, damage to the epithelial cells can disturb airway physiology through a number of different pathways. For instance, epithelial edema and shedding together with mucus production can cause airway obstruction and wheezing.

A number of proinflammatory cells such as monocytes, macrophages, and presumably dendritic cells are drawn into the area of infection by chemokines and local inflammation, and in turn secrete proinflammatory cytokines such as IL-1, IL-8, TNF- α , IL-10, and IFN- α and IFN- γ .²⁴⁻²⁶ These responses amplify the inflammatory response, and are also important antiviral effectors. In addition, changes in IL-8 and ECP levels in nasal secretions have been related to respiratory symptoms and virus-induced increases in airway hyperresponsiveness.²⁷⁻²⁹ These findings suggest that viral infections may cause recruitment of neutrophils and eosinophils to the airways of some infants and young children, raising the possibility that this unique host response is indicative of an increased risk for long-term asthma.

THE HOST IMMUNE RESPONSE IN VIRAL INFECTION IN CHILDHOOD

Immunologic risk factors have been identified through several different types of studies. Genetic analyses of children hospitalized with RSV infection have identified several polymorphisms of immune response genes that appear to increase the risk of severe RSV induced respiratory disorders.³⁰⁻³² A number of studies have performed immunological analyses at the time of a severe RSV infection, reduced peripheral blood mononuclear cell (PBMC) production of IFN- γ during months following RSV has been observed in children who develop subsequent asthma.³³ PBMC secretion of IL-10 has also been evaluated in infants hospitalized with RSV bronchiolitis. During the convalescent phase, IL-10 responses were significantly increased in wheezing patients and correlated significantly with the number of wheezing episodes.³⁴

Some prospective studies have evaluated the relationship of cytokine responses at the time of birth to the frequency of viral infections and wheezing illnesses. For instance, reduced IFN- γ secretion from mitogen-stimulated cord blood cells has been linked to an increased number of moderate to severe viral respiratory infections, and also to an increased risk of allergy.³⁵ These observations, together with evidence that antigen- and mitogen-induced Th1-like responses are immature during early infancy, suggest that delayed development in Th1 responses could increase the risk for bronchiolitis and atopy.³⁶

CONCLUSION

The immune and pulmonary systems of infancy are immature and are marked by an enhanced susceptibility to the effects of respiratory viruses. In addition to causing acute clinical illnesses such as bronchiolitis, severe lower respiratory infections can also have long-term effects that increase the risk of recurrent wheezing and chronic asthma. In getting older, viral infections continue to be the most significant source of asthma-related morbidity. Finally it is important to gain a better understanding the pathogenesis of virus-induced wheezing and early asthma in infancy for new and more effective treatments.

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