

Role of respiratory viral infections in the development of atopic conditions

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Purpose of review

Respiratory viral infections are implicated in both protection from, and inception of, allergic airway disease. Severe lower respiratory tract viral infections are associated with recurrent wheeze, asthma and atopy. It is unclear if this association is causal and the underlying mechanisms governing this are unknown. Whilst respiratory viral infections are the major precipitants of acute exacerbations of wheezing illness, early life infections are also clearly associated with protection from allergic diseases. This article aims to review the current understanding of the complex relationship between lower respiratory tract viral infections and their impact upon development of atopy in the airway.

Recent findings

Clinical studies and animal models have further demonstrated that lower respiratory tract viral infections are strongly associated with development of recurrent wheeze and asthma with human rhinoviruses being shown to be the most prevalent cause of lower respiratory tract viral infections in infants, along with associated asthma development. A case–control study provided evidence of a contributory role for respiratory viral infections within this association, whilst recent experimental studies provide a possible mechanistic insight.

Summary

Progress into understanding the relationship between respiratory viral infections and allergic airway disease is essential for development of treatments aimed at treating common risk factors mediating association but not cause. Recent findings may have begun to identify key pathways open to therapeutic intervention.

Keywords

allergy, asthma, respiratory syncytial virus, respiratory viral infections, rhinovirus

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Introduction

The prevalence of allergic airway disease and asthma in economically developed countries has increased significantly during the past 25 years [1], indeed asthma now affects over 150 000 000 people worldwide [2]. This increased incidence has been proposed to be explained in the past by the hygiene hypothesis. This hypothesis states that microbial exposure early in life drives maturation of the immune system toward a protective type 1 bias thereby preventing the development of allergic disease [3]. This implies that children growing up in modern, metropolitan society, with a low level microbial burden, will have poorly educated immune systems permitting the establishment of allergic responses and development of atopic conditions. The hypothesis has since undergone adaptation incorporating gene–environment interactions and the role of regulatory T cells to encompass the more complex combinations of all of the potential susceptibility factors. The capacity in

which respiratory viruses contribute within this framework, however, remains unclear.

Associations of respiratory viral infections and asthma

During the first few years of life the immune and pulmonary systems undergo a profound sequence of developmental changes. With these processes being potentially susceptible to modification it is quite possible that inflammatory responses, occurring during a respiratory viral infection, may orchestrate long-term structural and functional changes within the lung.

Wheezing due to lower respiratory tract illness is common in early life. These episodes are typically caused by viral infection, most frequently respiratory syncytial virus, rhinoviruses, parainfluenza viruses (PIVs), metapneumoviruses and influenza viruses, and are normally transient [4–7].

The question as to whether severe lower respiratory viral infection and bronchiolitis predisposes to the subsequent development of allergic disease or is merely indicative of at-risk, susceptible individuals remains unanswered.

Contrary to traditional belief that respiratory syncytial virus (RSV) is the most frequent cause of respiratory illness in infancy, recent studies have shown rhinoviruses to be the most prevalent infant respiratory viral infection [8] indicating rhinoviruses to be a major lower respiratory pathogen in early life [9]. Whilst RSV remains the most frequent cause of severe bronchiolitis, there is evidence to suggest that rhinovirus-induced bronchiolitis has the potential to be equally, if not even more, severe [10].

Earlier epidemiological studies have highlighted RSV infection as a major independent risk factor for the development of recurrent wheeze in the first 11 years of life [11]. Furthermore, RSV infection of a severe enough nature to require hospitalization has been shown to be associated with an increased and sustained risk for the development of atopy and asthma to 13 years of age [12]. A more recent study from the Childhood Origins of Asthma (COAST) study determined that within a population of children with an increased risk of developing asthma and allergies that the most significant risk factor for development of preschool wheeze was the occurrence of a symptomatic infant lower respiratory rhinovirus infection [13]. These findings have been further strengthened by a cohort study of children at high risk of atopy, demonstrating rhinovirus induced and RSV-induced wheezy lower respiratory tract infections in the first year of life to be significantly associated with recurrent wheeze at 5 years [14[•]]. This study reported that the increased risk was exclusive to children with early (<2 years) allergic sensitization, and this further refines our knowledge of associations between rhinovirus-induced wheezy lower respiratory tract infection within the first year of life and development of asthma by 5 years [14[•]].

Is there evidence of causation?

A similar study [15] reported earlier findings confirming an association between early life PIV or RSV infection and the development of possible asthma by age 2 years. The causal role of respiratory viral infections in development of allergic airway disease has been recently investigated in a case-control study of antiviral medication during the first year of life in preterm infants who have previously been shown to be at very high risk for RSV bronchiolitis and the later development of recurrent wheeze and asthma. The incidence of recurrent wheeze was monitored between 1½ and 3½ years of age in preterm infants who had received the anti-RSV monoclonal antibody palivizumab (which has been shown to have 78–80% efficacy in preventing RSV hospitalization) and who had not been hospitalized for

RSV and also in control children who had not received palivizumab, of whom around one third were hospitalized with RSV and two thirds were not. The study reported a 50% decrease in the incidence of recurrent wheeze in infants who received palivizumab compared with control infants, an effect which remained significant after adjustment for several potential confounding variables. The remaining 50% may possibly be attributed to other infections such as rhinovirus along with other common risk factors that might predispose to both increased susceptibility to respiratory viral infections (RVIs) and increased risk of asthma, such as impaired interferon production [16–18]. As the antiviral was only administered during the first year of life the method of protection was postulated as being via prevention against lower respiratory tract damage and small airway alterations during the most vulnerable period of time [19[•]].

Prospective randomized placebo controlled studies will be required to prove whether early life anti-RSV therapy does indeed have a protective effect against later development of asthma.

Mechanisms of virus induced asthma

Studies aimed at determining possible mechanisms of a causal link between viral infection and asthma development have focused on interplay between Th1 and Th2 responses.

Additional mechanistic insight into how acute antiviral Th1 immune responses influence the induction of chronic Th2 biased disease has recently been gained using mouse Sendai virus infection models. These studies showed that infection with the mouse paramyxovirus Sendai virus (SeV) led to increased type I interferon receptor-dependent expression of the high affinity IgE receptor, FcεRI, on dendritic cells within the lung during the acute antiviral response. Cross-linking of the FcεRI on dendritic cells resulted in CCL28 (MEC) production, subsequent recruitment of IL-13-producing CD4⁺T cells and development of mucus metaplasia [20^{••}]. This system demonstrates a potential mechanism by which viral infection can lead to an increase in Th2 responses. This effect may be more pronounced in individuals more genetically susceptible to allergic type responses. The authors state that the level of IgE production following SeV infection is dependent upon infection severity. The link between infection severity and the level of IgE production has been highlighted in other clinical viral infections, notably in dengue fever studies for which IgE levels were used as a prognostic marker of development of severe disease [21]. In addition, RSV-IgE responses correlated positively with increased frequency of recurrent wheeze [22]. An association between disease severity and magnitude of IgE response might help to explain why severe respiratory

viral infections are associated with an increased risk of asthma.

A protective mechanism for respiratory viral infections?

Population studies have repeatedly demonstrated that being a member of a large family [3] along with routine daycare attendance [23,24], both conditions suggestive of an increased frequency of viral infections during infancy, offer protection from the development of atopic disease and asthma in later life. It is proposed that repeated exposure to respiratory viruses can modulate development of the immune system, skewing immune responses away from an allergic type 2 response. Taking this further, recent studies in guinea pigs have shown that the presence of a Th1 background, whether genetic or induced, by CpG oligonucleotides, limits the development of downstream airways hyperresponsiveness and airway inflammation following RSV infection [25^{*}]. This further demonstrates the importance of host immune response in the context of development of airway pathology following RSV infection. Experimental mouse models incorporating infection and allergen sensitization have shown that during interactions between the two, the stimuli can crossregulate each other. Furthermore, outcome was shown to be very much dependent upon the timing of the events. For example, mice infected with RSV, establishing a Th1 dominant environment, 2 weeks or 2 days prior to sensitization with Japanese cedar pollen (JCP) had suppressed Th2-type responses subsequently induced as a consequence of the sensitization. In contrast, RSV infection 7 days following JCP sensitization did not have the ability to suppress the allergic type response, with JCP inoculation actually being shown to divert RSV responses from a Th1 phenotype to a Th2 via suppression of RSV-induced IFN- γ production and additional minor enhancement of JCP-induced Th2 cytokines [26]. It is clear that immune responses during a respiratory viral infection can modulate the bias and magnitude of even established responses to aeroallergens and, indeed, conversely, allergic responses have the ability to alter the course of antiviral responses. In understanding the complex interactions between infection and allergy, timing appears to be an important variable. Manipulation of the timing of allergen exposure and infection in experimental systems is a commodity commonly exploited, but this may not necessarily reflect the more continuous exposure experienced in daily life making interpretation of such, none-the-less important, studies somewhat difficult. It does appear that Th1 backgrounds associated with RVI have potential to suppress allergic responses, however, indicating that this could be a mechanism behind the protection associated with daycare or large families.

Conclusion

Respiratory viral infections may be able to orchestrate development of, or protection from, allergic airway disease. There is undeniable evidence that a strong relationship between viral infection during infancy and later recurrent wheeze and asthma exists. During the past year a number of interesting epidemiological studies have served to further confirm this association and emphasize the importance of rhinovirus as well as RSV. Some intriguing mechanistic studies have suggested possible mechanisms involved in both protection and disease induction. Finally, a case-control study suggested early life anti-RSV therapy may confer protection against risk of asthma development in high-risk infants. The lack of placebo controlled therapeutic intervention studies aimed at reducing viral replication, however, has prevented a definitive judgement on the exact role of respiratory viruses in inception of allergic disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 201–203).

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