Published in final edited form as:
Curr Respir Med Rev. 2011 June 1; 7(3): 160–166.

Rhinovirus-associated wheeze during infancy and asthma development

Tuomas Jartti, MD[1] and **James E. Gern, MD**[2]

[1]Department of Pediatrics, Turku University Hospital, Turku, Finland [2]Departments of Pediatrics and Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Abstract

Rhinovirus is commonly associated with bronchiolitis - only second to RSV during the first year life. The prevalence of HRV-bronchiolitis may be very high in predisposed infants. HRV diagnosis is almost exclusively based on PCR, which detects respiratory infections with or without symptoms. Two immunologic factors, interferon responses and atopy, have been associated with susceptibility to HRV-bronchiolitis in multiple studies. The current data supports the hypothesis that susceptibility to HRV-bronchiolitis is likely to be an early manifestation of biased immune responses, which are linked to both decreased viral defence and atopic airway inflammation. Prospective studies have consistently shown that early wheezing associated with HRV infection is closely associated with recurrent wheezing and the development of asthma in children. Collectively, these studies suggest that HRV infection in wheezing children could serve as a clinically useful marker for early identification of asthma prone children. The findings to date provide the rationale for future studies to incorporate rhinovirus illnesses into asthma risk indices.

Keywords

Wheezing; bronchiolitis; asthma; rhinovirus; respiratory syncytial virus; prognosis; infant; child

Introduction

Population-based birth cohort studies have shown that wheezing during lower respiratory tract infection is most common during first year of life [1–4]. The prevalence of wheezing has been 18–32%, 9–17% and 4–12% in the first, second and third year of life, respectively [1, 4]. In addition, younger infants are at higher risk than older infants for requiring hospitalization for wheezing [5].

Risk factors for bronchiolitis include premorbid lung function [1, 6–8], innate and acquired immune responses [9–12], genetic factors (limited mainly to RSV induced disease) [11–16], attendance in day-care or number of older siblings [1–3, 17], and environmental tobacco smoke, especially maternal smoking during pregnancy [2, 18–20]. Other environmental factors linked to the risk of bronchiolitis include exposure to air pollution [21], dampness in the home environment [22] and antibiotic exposure in early life [23]; and young maternal age, low maternal occupation level and low household income level are associated with bronchiolitis in some studies [17, 24]. Although acute respiratory tract infections are equally

Correspondence to: Tuomas Jartti, Department of Pediatrics, Turku University Hospital, P.O. Box 52, FIN-20520 Turku, Finland; Fax: +358 2 313 1460; phone: +358 40 7270 284; tuomas.jartti@utu.fi.

The authors have no conflict of interest in connection with this paper.

common in males and females [25, 26], acute wheezing is more common in boys [4, 17, 24, 27, 28]. In most studies, breastfeeding has been protective for wheezing illnesses in infancy [2, 17, 29]. Infants born prematurely or those who have congenital heart disease or chronic lung disease are at the highest risk of requiring hospitalization for bronchiolitis [5].

Allergic individuals may have impaired antiviral responses, leading to more severe infections and wheezing [30–36]. It has been proposed that a subgroup of infants with early respiratory allergy and eosinophilic inflammation in the airways is particularly prone to wheeze during rhinovirus infections [11, 37]. In this review, we focus on rhinovirus associated bronchiolitis, and will review its etiology, diagnostics, co-factors and predictive value for the development of asthma.

What is the prevalence of HRV-bronchiolitis?

Wheezing illnesses in young children are almost exclusively (up to 95%) associated with respiratory viral infections [38, 39]. Respiratory syncytial virus (RSV) dominates in bronchiolitis during the winter months. The overall prevalence of RSV-bronchiolitis depends on yearly epidemics, but it may be up to 80% in infants aged less than 3 months and rapidly decreases there after [40, 41]. The first RSV infection usually causes more severe illness in a non-immune infant whereas subsequent infections usually cause milder symptoms.

In older wheezing children, the common cold virus rhinovirus (HRV) is most often detected – the breaking point in dominance between HRV and RSV is around 12 months in hospitalized wheezing children [40]. The prevalence of HRV-associated wheezing increases with age; approximately 20–40% in infantile bronchiolitis, and increasing to about 50% of hospitalized wheezing children by age 36 months, and about 50–85% in older wheezing children or in children with exacerbation of asthma [40–42]. The susceptibility of HRV-bronchiolitis seems to be linked to predisposition, since the prevalence of HRV bronchiolitis has been up to 50–80% during the first year of life in recurrently ill infants of atopic families [43].

One particular feature of HRV is that there are at least 100 circulating HRV serotypes [44, 45]. Moreover, new sensitive molecular typing assays have revealed that there are over 50 distinct HRV strains in the newly described HRV-C species [46–48]. Rhinoviruses elicit serotype specific antibody responses, and recurrent HRV infections are typically caused by different strains [43].

What does positive HRV PCR result mean?

The development of PCR techniques for virus detection in the 1990s has expanded our view of the epidemiology of viral respiratory infections [49]. In cross-sectional studies of subjects with respiratory symptoms, detection rates by PCR have been as high as 85–95% (or even 100% in certain subanalyses) [38, 41, 42, 50–52]. This increase is mainly the result of the development of PCR diagnostics for respiratory picornaviruses, HRV and enteroviruses, and newly discovered viruses such as human bocavirus, human metapneumovirus and new coronaviruses. At the same time, the interpretation of positive PCR results has been made more difficult by multiple co-existing viruses in symptomatic subjects (up to 43%) and by high virus detection rates in asymptomatic subjects (up to 40–68% in young children during high prevalence seasons) [41–43, 53–55]. In a recent comprehensive review of literature from 1965 to present, the mean prevalences of HRV, adenovirus and RSV in respiratory samples of asymptomatic subjects were higher when detected by PCR than those found by conventional methods: HRV 15% (365/2416) vs 1.5% (255/14669, $p < 0.0001$), adenovirus 5.3% (103/1958) vs 1.8% (40/2175, $p < 0.0001$) and RSV 2.6% (51/1974) vs. 0.7%

(23/3175, $p < 0.0001$). These findings attest to the increased sensitivity of new molecular diagnostics, but also raise concerns about the clinical significance of these positive viral findings when detected solely by PCR [49].

Rhinovirus is usually the most frequently detected virus regardless of the presence of symptoms. HRV diagnosis relies almost entirely on PCR because this virus is difficult to culture, there is no antigen detection test available and serology is not feasible. Several findings have demonstrated the clinical relevance of PCR-positive HRV findings. First, three recent studies showed HRV to be more prevalent in children with respiratory symptoms (mainly wheezing) when adjusted or compared with the findings in asymptomatic children/phases [43, 56, 57]. Second, it has been shown that HRV can replicate in cells of the lower respiratory tract and persist for more than a year in the lower respiratory tract of immunocompromized patients [58–60]. Third, the prevalence of recurrent or persistent HRV infections has been low (3–4%) in studies that genotyped the virus [43, 60]. Also, findings from studies without genotyping suggest that respiratory picornavirus infections are of rather short duration in immunocompetent subjects whether symptomatic or not [61–63]. Fourth, HRV PCR positive findings correlate with systemic immune responses in young wheezing children [64]. Finally, an immune host may not develop symptoms. Among young children, however, mild symptoms (e.g. sore throat, malaise) may not be verbalized, or easily recognized by the parent or physician [65]. Although it is known that replication of viruses in the respiratory tract can last longer than illness [66], only 20–40% of viruses detected in asymptomatic subjects can be linked to previous (10 days to 4 weeks) or later (7 to 10 days) development of respiratory symptoms [61, 62, 67]. These findings argue against the suggestion that viruses detected by PCR in asymptomatic subjects are residual nucleic acids left over from distant respiratory infections. Instead, the data suggest that PCR detection is likely to reflect true respiratory infections with or without symptoms.

Which factors are linked to HRV-bronchiolitis?

Two immunologic factors, low interferon responses (especially low interferon-gamma [IFN-γ]), and indicators of atopy (eosinophilia, allergen-specific IgE), are closely associated with susceptibility to HRV-bronchiolitis in multiple studies [37]. Experimental and clinical data indicate that interferon responses in early life are inversely associated with the severity of viral respiratory illnesses [31]. For example, there is clinical evidence that babies with low ex-vivo interferon responses in early life are more likely to have frequent viral respiratory illnesses, including those associated with wheezing [9, 34, 35]. In addition, airway epithelial cells cultured from patients with asthma were reported to produce reduced amounts of IFN-β, IFN-γ, and IFN-λ in response to HRV and support enhanced viral replication [31–33, 36]. This concept is controversial, because other studies of isolated epithelial cells have not found asthma-related differences in HRV replication [68–70]. In addition, viral shedding is similar in volunteers with and without asthma after experimental inoculation with a safety tested strain of HRV-16 [36, 71]. Still, these data suggest the possibility that impaired interferon responses, either systemically or in the airways, could increase the risk of more severe viral respiratory infections in infancy and perhaps promote long-term damage to airway structures. Interestingly, reduced IFN-γ responses in infancy are also observed in children with atopic features, which could help to explain why atopy is a risk factor for virus-induced wheezing and the progression to asthma (Figure) [37, 72, 73].

Four previous studies have linked HRV-induced wheezing in infancy to allergic sensitization, nasal and systemic eosinophilia, and clinically diagnosed atopic eczema [41, 72, 74, 75]. The presence of respiratory allergen-specific IgE and high total IgE is a risk factor for viral wheeze in children presenting for emergency care [76, 77]. These findings are supported by a case-controlled study of children admitted for asthma exacerbations in

which detectable virus, allergic sensitization, and high allergen exposure were synergistic risk factors for asthma hospitalization in children [6]. The exacerbation group also had fewer subjects using inhaled corticosteroids compared to children with stable asthma. These data are not entirely consistent since Rakes et al. (1999) reported a link between eosinophils and HRV wheezing illnesses, but they also reported that HRV-negative wheezing children had higher rates of allergic sensitization than HRV-positive wheezing children [41]. Finally, a *post hoc* analysis of experimental HRV infections in adult subjects with mild asthma revealed that those with high levels of total IgE had greater lower respiratory tract symptom scores than the low IgE group [78].

In the long-term follow-up studies assessing the development of asthma, the interaction between atopy and susceptibility to HRV-bronchiolitis has been less clear. Hyvärinen et al. (2005) and Kusel et al. (2007) found that the relationship between HRV wheezing and subsequent childhood asthma was dependent on early onset of atopy [72, 79]. On the contrary, Lehtinen et al. (2007) and Jackson et al (2008) found HRV associated wheezing to be independent risk factor for asthma at ages 2–6 years [73, 80].

How does allergic sensitization increase risk for HRV associated wheezing?

There are several mechanisms that could explain why allergic sensitization increases the severity of HRV infection in the lower airways. First, atopic inflammation may increase the expression of the major HRV receptor, ICAM-1 (intercellular adhesion molecule 1) [81]. For example, IL-13 and other T-helper$_2$ cytokines have been shown to increase expression of ICAM-1 on an epithelial cell line *in vitro*, which resulted in increased viral titers after HRV infection [81]. Moreover, epithelial cells recovered from nasal brushings of atopic subjects express significantly higher ICAM-1 levels than those from healthy controls, and increased ICAM-1 expression with allergen exposure was inducible only in the epithelial cells from atopic subjects [82]. In agreement with these findings, atopic individuals have shown more severe illnesses after experimental HRV inoculation[41, 83], although there are also contradictory reports [30, 84]. This mechanism does not apply to minor HRV group, or HRV-C species strains that presumably bind to unique cellular receptors.

Second, T helper$_2$ (Th$_2$) cell polarized immune responses can counteract Th$_1$ responses such as interferon- γ, which potentiates innate antiviral responses [9, 31–36]; subjects with low interferon responses have more severe vral respiratory illnesses as mentioned above. Third, disrupted airway epithelium may favor HRV replication as shown in recent *in vitro* studies [85]. Interestingly, damaging airway epithelium allowed HRV to access deeper cell layers that express increased amounts of ICAM-1 and support greater HRV replication. Also, poorly differentiated epithelial cells may be more susceptible to HRV infections than intact layers of well-differentiated epithelial cells [86]. Airway epithelium could be damaged by allergic inflammation, repeated respiratory infections, and/or by air pollution. Finally, HRV associated wheezing increases with age as does atopy[40]. Thus, virus/allergen interactions are likely to be stronger as childhood progresses. Overall, atopy is a common condition in asthma, with allergic rhinitis occurring in as many as 80% of older children and young adults with asthma [77].

What is the prevalence of asthma symptoms after early childhood wheezing?

According to the International Study of Asthma and Allergies in Childhood (ISAAC), the global prevalence of wheezing is 11.5 %, and frequent or severe asthma symptoms occur in 4.9 % of children at the age of 6–7 years [87]. The respective numbers are 14.1 % and 6.9 %

for 13–14 years old children [87]. The reported prevalence rates of asthma symptoms vary considerably; the rates of frequent asthma symptoms in the developed countries are highest in Australia and New Zealand (8.4–12.1%), and lower in Eastern Europe (3.2–6.2%).

Depending on the study design and length of follow-up, approximately one-third of infants who wheeze in the first three years of life continue to wheeze after the age of three years [4, 88, 89]. Even a mild wheezing episode during infancy is a significant risk factor for wheezing and asthma later in life. Prospective birth-cohort-studies, have shown that about 30% of infants who wheeze in early life continue to report wheezing symptoms in the pre-school years [3, 4, 88, 90, 91]. A retrospective population-based study, which applied a health-care specialist-confirmed diagnosis of bronchiolitis, revealed that 16% of infants with an outpatient visit for bronchiolitis at less than one year of age had frequent wheezing symptoms or asthma at age 4–5.5 years [92]. In a prospective high-risk birth cohort study, which included only children with an atopic predisposition, the risk of frequent symptoms or asthma at age 6 was 30–60 %, depending on the viral aetiology of early wheeze [73]. After hospital admission for wheezing in infancy 18–53 % of pre-school children experience frequent symptoms or asthma, and the prevalence of school-age asthma, at 7.6–9.5 years of age, has been 15–40 % [93–97].

What are the early predictive factors for asthma?

Early predictive factors of asthma mainly include atopic eczema, parental asthma, allergic sensitization and eosinophilic inflammation [91, 98, 99], but also low lung function in infancy [8], bronchial hyperreactivity at least in atopic infants during early life [100, 101] and higher age when wheezing occurs (Figure) [1]. Exposure to tobacco smoke in utero and in infancy reduces lung function in infancy and impairs postnatal lung function development [102–106]. Birth cohort studies evaluating effects of early pet exposure on subsequent asthma have yielded inconsistent results [3, 107–110]. It has been proposed that exposure to microbes associated with barn dust, furred animals and livestock early in life may protect agiainst the development of allergies and asthma [109, 110, 111].

Asthma is a heterogeneous condition, and currently there is no single predictive marker available that can identify those wheezing infants who are at high risk of developing asthma. Therefore, a combination of clinical characteristics and simple biological markers has been created to form algorithms, which may identify, at an early stage of the disease, high risk for asthma. Castro-Rodriquez et al. introduced the first algorithm known as the “asthma predictive index” (API) [97]. The API was later modified for the use in a pharmacological trial for secondary asthma prevention (mAPI) and to be applied to hospitalized wheezing children (hAPI) [98, 112]. In general, the API and mAPI have good specificity, but relatively low sensitivity. Aeroallergen sensitization is not feasible as an early risk factor for asthma in infants since it is rare during early life even in wheezing children [40, 91]. Improved predictive algorithms for infants are therefore needed.

What is the long-term outcome of HRV-bronchioltis?

Several recent observations highlight HRV wheezing illnesses in young wheezing children as an important predictive factor for recurrent wheezing or asthma [39, 73, 80, 113]. In population based studies on young hospitalized children with acute wheezing, HRV infection has been associated with recurrent wheezing (≥3 physician confirmed episodes) during a 12-month follow-up period after the first episode (hazard ratio 5.1, 95% confidence interval 1.0–25, vs. RSV positive cases) and with the development of asthma at school-age (odds ratio 4.1, respectively 1.0–17, vs. HRV negative cases) [80, 113]. In outpatient populations at increased risk for atopy based on family history, more than one wheezing HRV illness during infancy increased the risk for third year wheezing (odds ratio 10, 4.1–

26) and modestly increased the risk for asthma at age 6 years (odds ratio 2.8, 1.1–7.5) [39, 73]. Interestingly at the third year of life, wheezing with HRV was markedly associated with asthma at age 6 years (odds ratio 26, 8.2–80) [73]. Nearly 90% of children who wheezed with HRV in year 3 had asthma at age 6 years. In the same study, aeroallergen sensitization during infancy and at age 3 years only modestly increased the risk for asthma at age 6 years (odds ratios 3.4 and 3.6 respectively) [73]. In another study on a high risk cohort, wheezing with HRV during the first year of life was associated with wheezing at age 5 years (odds ratio 3.2, 1.1–9.5) [72]. Comparable findings were made for current asthma. Strikingly, these associations were restricted to children who displayed early sensitization (≤2 years old).

Short courses of systemic corticosteroids are one of the cornerstones of the management of acute asthma in children, but their efficacy among young wheezing children has remained obscure. RSV bronchiolitis does not respond to systemic corticosteroids [114–116], but few studies have tested for specific subgroups of patients who do respond. One study evaluated the efficacy of systemic corticosteroid in relation to HRV etiology among young first-time wheezers [75, 80]. A 3-day course of oral prednisolone decreased the probability of recurrent wheezing (≥3 physician-confirmed episodes) in children with eczema (hazard ratio 0.2, 95% confidence interval 0.0–0.6) and HRV (respectively, 0.2, 0.1–0.7) in this *post hoc* analysis. Prednisolone decreased recurrent wheezing by 48% over a 12-month study period in these first-time wheezers affected by HRV. The authors speculated that the efficacy of prednisolone may be related to pre-existing airway inflammation that may predispose to HRV infection and is associated with eczema.

Conclusions

Rhinovirus is commonly associated with bronchiolitis, and is second only to RSV during the first year of life. The prevalence of HRV-bronchiolitis may be even higher in predisposed infants. HRV diagnosis is almost exclusively based on PCR, which is likely to detect true respiratory infections with or without symptoms. Two immunologic factors, interferon responses and atopy, have been associated with susceptibility to HRV-bronchiolitis in multiple studies. These findings supports the hypothesis that susceptibility to HRV-bronchiolitis is likely to be an early manifestation of biased immune responses, which could be linked to both decreased viral defence and atopic airway inflammation. Accordingly, prospective studies have consistently shown that early wheezing associated with HRV infection together with early onset of atopy are closely associated with recurrent wheezing and the development of childhood asthma. Collectively, these studies suggest that HRV infection in wheezing children could serve as a tool for early identification of asthma prone children. The findings to date provide the rationale for future studies to incorporate early HRV wheezing episodes into an improved asthma risk index [117].

Acknowledgments

Supported by the Academy of Finland (Grant numbers114034 and 132595), the Foundation for Pediatric Research, both in Helsinki, Finland, and NIH grants.

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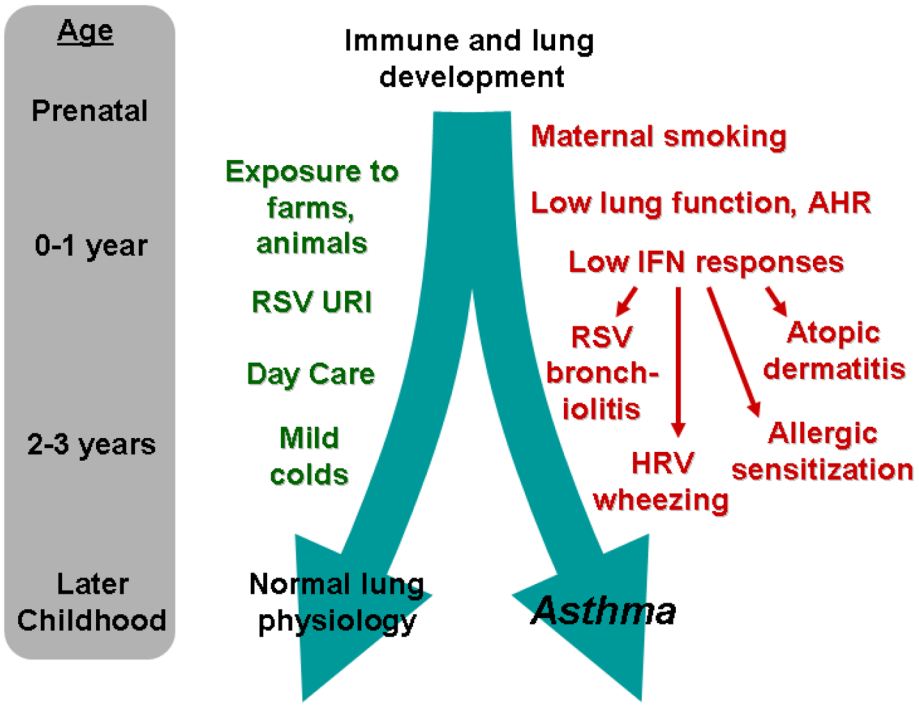

Figure 1.
Early life influences on the development of asthma. Development of the lungs and immune system are initially influenced by genetics and prenatal factors, and later by a number of environmental and lifestyle factors in the first few years of life. Exposure to farm environments, furred animals, and day care in early life can reduce the risk of asthma. In contrast, low interferon responses, wheezing with respiratory viruses, and the development of atopy indicate an increased risk for subsequent childhood asthma.