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EDITORIAL

Rhinoviruses: markers of, or causative for, recurrent wheeze and asthma?

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Rhinovirus (RV) infections occur early and recurrently in life and impose a large burden of disease in infants and young children [1–3]. RVs are the most frequent pathogens detected during both upper and lower respiratory tract infections and are associated with a large spectrum of clinical outcomes in this age group [4, 5]. In the very young, they are one of the leading agents of bronchiolitis, second only to respiratory syncytial virus (RSV), and in children aged >12 months of age they are predominant pathogens associated with wheezing episodes [6–8]. In addition to their impact on short-term morbidity, RVs have been shown to represent an important pathogenic factor in the development of recurrent wheeze and asthma; a role which is yet not fully understood [9–12]. Several studies have been conducted over the past few years evaluating the influence of RV infections in early life on the development and incidence of wheezing and asthma [13–17]. They have clearly demonstrated that RV-associated wheezing is a risk factor for asthma development, and that approximately one third of infants with recurrent RV-induced wheezing illnesses go on to develop asthma. Unfortunately, most of these studies have been conducted in infants at high risk for atopy and asthma and not in unselected populations, or have included hospitalised children of a wide age range. These are significant limitations in the understanding of the respective influences of virus infections, atopy, age and maturity of the immune system on asthma development on a population level.

In this issue of the *European Respiratory Journal*, MIDULLA *et al.* [18] present a prospective, single-centre study in which they assessed possible risk factors for recurrent wheezing during a 1-yr follow-up in >300 infants aged <12 months hospitalised for their first episode of bronchiolitis. They found that RV-induced bronchiolitis (OR 3.3, 95% CI 1.0–11.1) and a positive family history for asthma (OR 2.5, 95% CI 1.2–4.9) were the strongest independent risk factors for recurrent wheezing and, therefore, concluded that a nasal washing positive for RV in infants hospitalised for bronchiolitis can possibly predict infants prone to the development of recurrent wheezing. These results concur well with a very recently published Finnish study in the *European Respiratory Journal* [19], in which children <6 months of age hospitalised for bronchiolitis were followed at 6 yrs of age, demonstrating that the risk of asthma was lower after RSV bronchiolitis (8%) than after bronchiolitis caused by other viruses (24%). It will be interesting to see whether RV-induced bronchiolitis in the cohort of MIDULLA *et al.* [18] remains a risk factor for the development of asthma at school age.

One of the strengths of the study by MIDULLA *et al.* [18] is that the authors investigated a clinically homogenous and well-characterised cohort of unselected infants. They included infants <12 months of age with a first episode of bronchiolitis, which was defined as an upper respiratory tract infection followed by acute onset of respiratory distress with cough, tachypnoea, retractions and diffuse crackles on auscultation. Thus, they avoided the pitfall of using wheezing as an entry criterion when the study outcome is also wheeze. Bronchiolitis is a clinical diagnosis without common international definition, which makes comparisons between studies, and especially assessment of factors, such as those predisposing to the development of asthma or predicting response to treatment, difficult [8]. Whilst in Europe the presence of inspiratory crackles on auscultation is regarded as an important definition criterion for bronchiolitis, and an upper limit of age of 12 months is usually chosen, the definition is applied more broadly to a first episode of acute viral wheeze within the first 2 yrs of life in North America [20]. Thus, early presentations of asthma are likely to overlap with the North American definition of bronchiolitis, which has major implications with regard to the understanding of the pathophysiology of asthma, but also with regard to treatment responses, for instance to steroids or inhalation with hypertonic saline [21, 22]. Therefore, a European Respiratory Society/American Thoracic Society Task Force on the definition and treatment of bronchiolitis is imperatively needed to address these issues.

The study by MIDULLA *et al.* [18] also has shortcomings, which have to be considered when interpreting their findings. Besides the fact that the authors relied on parentally reported recurrent wheeze, which is at best imperfect [23], the detection rate of RV in their study was low (only 24 out of 313 infants), and as such the estimates of association were rather weak, with wide confidence intervals and only borderline statistical significances. In addition, there was a significant drop-out rate, with a high RV detection rate in the sub-cohort that was lost due to follow-up (five out of 51 infants). A few more RV-positive infants in the non-wheezing group would have made the study results no longer significant.

What still remains unanswered is the question as to whether RVs are directly involved in the development of childhood wheeze and asthma or whether they only represent a proxy for infants prone to developing obstructive lung diseases. These two scenarios are not mutually exclusive, but the fact that only some

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infants with RV-induced bronchiolitis go on to develop recurrent wheezing and/or asthma later in life suggests that other than viral factors must play a role in this process. Airway dysfunction could be a direct consequence of RV infections in early life, for instance through damage to the airway epithelium and the initiation of inflammatory and remodelling processes [10, 12]. As the clinical presentation, dynamic of infection and immune responses differ according to rhinovirus species [24], it could be speculated that their respective influence on the development of recurrent wheeze and asthma varies. With respect to this, it would have been interesting to investigate the effects of the recently described RV-C species [25] in the study by MIDULLA *et al.* [18], but numbers were too small for such analysis. Host factors influencing susceptibility towards RV infections are numerous and include genetic factors [26], reduced pre-morbid lung function [27], impaired immune responses towards viruses [28, 29] and atopy [13, 14]. The interplay of these factors is complex but most studies, including the current study by MIDULLA *et al.* [18], suggest that the highest risk for developing asthma is observed in children having both recurrent viral infections during infancy and atopic features, such as atopic dermatitis, early sensitisation to food or inhaled allergens, eosinophilia or a maternal history of allergy. Additionally, the timing and the frequency of RV infections with regard to the individual phase of immune development also seem to play an important role in this process. As infancy is a period of profound growth and development of the pulmonary and immune system, RV infections and associated inflammatory and remodelling processes occur during a vulnerable phase of ongoing developmental processes, which might be thus interrupted and/or disrupted [30].

Taken together, viral aetiology, host susceptibility (in particular allergic predisposition and sensitisation), and illness severity, timing and frequency all might contribute as synergistic factors to the risk of developing asthma. To disentangle these complex interactions, carefully conducted longitudinal and prospective population-based studies in unselected healthy infants are needed. They may allow us to more precisely define the relationships and underlying mechanisms linking RV infections in early life and development of recurrent wheeze and asthma in childhood, and ultimately lead to better targeted preventive and therapeutic measures for these conditions.

STATEMENT OF INTEREST

None declared.

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