Early identification of atopy in the prediction of persistent asthma in children

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See Editorial page 1009

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The long-term solution to the asthma epidemic is thought to be prevention, and not treatment of established disease. Atopic asthma arises from gene–environment interactions, which mainly take place during a short period in prenatal and postnatal development. These interactions are not completely understood, and hence primary prevention remains an elusive goal. We argue that primary-care physicians, paediatricians, and specialists lack knowledge of the role of atopy in early life in the development of persistent asthma in children. In this review, we discuss how early identification of children at high risk is feasible on the basis of available technology and important for potential benefits to the children. Identification of an asthmatic child's atopic status in early life has practical clinical and prognostic implications, and sets the basis for future preventative strategies.

Asthma-related phenotypes in childhood

International research over the past 20 years has established gene–environment interactions as the basis of the most common form of asthma, atopic asthma.[1] Current treatment strategies do not alter the long-term prospects for children with asthma, despite controlling symptoms and improving quality of life,[2] therefore implying that a different approach is necessary.

Several epidemiologically distinct wheezing phenotypes have been identified in childhood,[3] the most common being: transient infantile wheeze, in which children have recurrent wheeze during the first 2–3 years of life but rarely afterwards; viral-associated wheeze, in which children typically have episodic wheeze associated with respiratory viral infections and may not wheeze at other times; and atopic asthma, in which children have wheeze associated with sensitisation to aeroallergens and frequently have signs of other atopic diseases, such as dermatitis and rhinoconjunctivitis. Although all these wheezing phenotypes are a burden on families and the community, asthma that persists throughout childhood and into adulthood is the greatest burden and, therefore, is the major target for prevention programmes. Here, we use the term persistent asthma to describe a disease that persists from early childhood into adult life, and is not a description of symptoms as for staging asthma in clinical guidelines. Association between asthma and sensitisation to aeroallergens continues through childhood into the teenage years,[4–11] and, in many cases, into early adulthood,[12] at least in the developed world.[13]

Search strategy and selection criteria

The Medline search engine was used to find articles in the PubMed database, with the search terms "childhood asthma", "allergic sensitisation", "longitudinal cohort studies", and "asthma risk factors". In addition to this search, we looked for articles relevant to the Review. We did not use any selection or rejection criteria.

Physiologically, wheeze implies expiratory flow limitation, but this symptom does not give any clue about the underlying cause. Any insult that decreases airway diameter or alters airway wall compliance could lead to wheeze. Wheezing is more common in the first years of life in boys.[4] One possible mechanism for this sex difference is that male children might have smaller airways than female children in relation to lung size;[14] however, direct proof is lacking. Wheezing associated with viral infections is common during childhood, especially during the first years of life. Viral lower respiratory infections are likely to result in wheezing if they induce inflammation and oedema of the airway epithelium, decreasing airway diameter. At least 20% of all children have one or more episodes of lower respiratory infection with wheezing in the first year of life, and up to 90% of these episodes are associated with documented viral infections.[15] 30% of children enrolled in the Tucson Children's Respiratory Study[3] had one or more lower respiratory infection associated with wheezing in the first 3 years of life. Cohort studies[16–20] in different parts of the world have shown that such lower respiratory infections associated with wheezing are most commonly caused by rhinoviruses, respiratory syncytial virus, parainfluenza viruses and, to a lesser extent, adenoviruses, human metapneumovirus, and influenza virus.

Symptoms in most children with viral-induced wheeze disappear in early school years.[21,22] These children generally have normal spirometry and are commonly non-atopic.[21] By contrast, children who become sensitised to common aeroallergens are likely to retain symptoms and have lower lung function at school age.[3,10,16,21] In a group of children enrolled between the age of 7 years and 17 years, and reassessed 6 years after enrolment, those with either persistent or new atopy to house dust mites had lower lung function than those who remained unsensitised. Loss of lung function was greater in those with persistent atopy than in those with new onset of atopy.[23] Furthermore, loss of lung function reported

during the first 6 years of life[3] continued in allergic asthmatics during adolescence.[24] Longitudinal follow-up of birth cohorts in Europe, USA, and Australia shows that early sensitisation[10,16,21,25,26] and severe sensitisation[27] are risk factors for persistence of asthma. However, although transient sensitisation conveys increased risk of wheezing,[10] risk for persistence of symptoms is more pronounced if sensitisation itself is also persistent.[10,21,28] Enhanced risk of asthma associated with early sensitisation may be related to the association of early sensitisation with more intensely T-helper-2(Th2)-cell-polarised long-term memory responses,[29] interactions with other risk factors during early postnatal period, or both.

The role of the environment: a differential response to allergen and bacterial products

A recent prospective cohort study[30] assessed postnatal development of lung function in children at high risk of persistent asthma raised in conventional household environments in the UK (control) versus those raised under strict environmental control to reduce exposure to indoor allergens and airborne irritants. Although controlled environments did not improve sensitisation rates, children living in these environments had better lung function at 3 years of age than children in the control group. Lung function was not different between the two groups at 4 weeks of age, indicating that this was a postnatal effect. These data suggest that the pro-inflammatory standard environment was associated with decreased lung growth. The significance of these findings is not known, but studies[31,32] have shown that reduced lung function in early life is an independent risk factor for persistent asthma. The mechanisms underlying these effects of early environmental control are incompletely understood, but the clear association between indoor allergen concentration and frequency of wheezing episodes,[10,21,33] or development of new sensitisations, persistent bronchial responsiveness, and doctor-diagnosed asthma[34] in sensitised individuals suggests that reduction of allergen exposure, leading to decreased allergy-mediated airway inflammation, may be one factor.

Atopic sensitisation also increases the susceptibility of the airways to non-allergenic, but nevertheless pro-inflammatory, components of house dust, such as microbial lipopolysaccharides,[35] and reduced exposure to these in early life may be a contributing factor. Exposure to lipopolysaccharides before sensitisation is associated with reduced risk for sensitisation.[36] Active exposure to immunogenic aeroallergens seems to be a prerequisite for the development of normal immunological tolerance, which provides protection against de novo sensitisation.[37] Therefore, understanding the relevance of exposure to these agents to asthma pathogenesis in children can only be gained with the knowledge of children's current atopic status.

Respiratory viral infections: direct and atopy-dependent roles in asthma development

Most wheezing episodes in the first few years of life are due to viral infection. Acute lower respiratory infections, including bronchiolitis, resulting from rhinoviruses and respiratory syncytial virus, account for most admissions to hospital of children younger than 3 years.[20,38] The mechanisms underlying wheeze-promoting effects of these infections are only partly understood, but are associated with the spread of infections to the lower airways and subsequent intensification, possibly resulting in inflammatory damage of airway tissues. Studies in animals[39] support a role for neurogenic inflammation, caused by respiratory syncytial virus infection.

The contribution of individual inflammatory mechanisms to the response of the host to respiratory viruses is controversial (eg, respiratory syncytial virus). A prominent contribution from recruited neutrophils to the response against respiratory syncytial virus in the airways of infants has been reported,[40,41] but the role of these cells in viral clearance is unknown.[40] An underlying role of Th2 cells in the lung response against respiratory syncytial virus in the form of local IgE production has also been documented.[42] Th2-cell response has become a repeating theme in much of the published data for respiratory syncytial virus infection in children and in murine models, particularly in relation to the possible link between Th2-cell-dependent eosinophil responses and infection severity. Reports of this effect include the presence of eosinophil secretory products in airway secretions of infants during acute infection,[43–46] the presence of eosinophils in nasal secretions,[46] and accompanying changes in the activation status of eosinophils in the blood.[47,48]

Circulating eosinophil numbers transiently drop during acute infection by respiratory syncytial virus,[48–51] which indicates active migration to the site of infection. The possibility that such recruitment may be a part of the host's normal antiviral defence response in children under 3 years of age[50] is indirectly supported by recent findings from a murine model of respiratory syncytial virus showing that eosinophils accelerate viral clearance via a Toll-like-receptor-7-dependent pathway.[52] Cytokine-receptor expression on blood-borne eosinophil precursors in infants substantially differs from the interleukin-5-dominant pattern typical of school-age children, and is characterised by receptors for the ubiquitous interleukin-3 and granulocyte macrophage-colony stimulating factor,[53] which are so-called first-line cytokines produced early in most classes of cellular immune responses, including those against pathogens. These cytokine responses may contribute to the increased relevance of eosinophils in inflammatory exudates in early life.[53,54]

Severe viral bronchiolitis is more frequent in infants with elevated IgE concentrations,[46,55] suggesting that predisposition to both states may be associated with common genetic or epigenetic mechanisms.[1] These

factors may act together with others implicated in innate mechanisms (such as type III interferon production) more specifically related to host antiviral defence.[56] Severe asthma exacerbation in children older than 2 years is commonly associated with respiratory viral infections, and the most susceptible subgroups include those sensitised to aeroallergens.[20,57–60] These and other findings suggest that inflammatory pathways triggered by viral infections and inhalant allergy can function independently or in combination to worsen asthma symptoms in individuals with established disease.[1,20]

The results of some prospective cohort studies that have followed up large groups of children over various periods indicate that the effects of these inflammatory pathways are not restricted to asthma exacerbations but may also be key to disease aetiology. Most early studies in this area[5] mainly focused on the role of atopy in isolation, whereas recent prospective birth cohort studies[3,9,10,16,21,22,61] have assessed both the role of atopy and viral infections in asthma aetiology. Overall, findings are consistent with a two-hit model for asthma[1] in which airway inflammation triggered by viral infection or allergy during postnatal lung growth disrupts underlying tissue differentiation programmes, leading to anomalies in respiratory function, which last for long periods later in life.[1,62] Although both allergy and respiratory infections during early life are independently associated with risk for subsequent development of asthma, the highest odds ratios for persistent asthma are seen in children who have both[1,9] (figure).

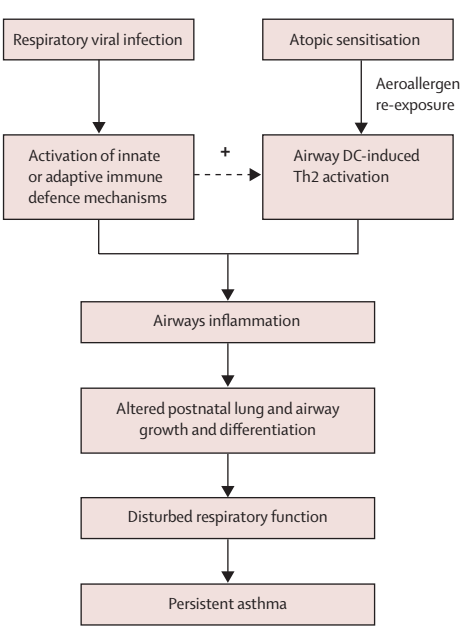

Figure: **Interactions between early respiratory viral infections and atopic sensitisation on the pathway to persistent asthma**
The link between activation of immune-defence mechanisms to viral infections and activation of airway dendritic cells is shown. DC=dendritic cell. Th2=T-helper-2 cell.

Interactions between atopy and infections in this context are unclear. In a cohort at high risk, the finding that early infections by rhinoviruses or respiratory syncytial virus give the greatest risk to develop persistent asthma in children who are sensitised by 2 years of age suggests that the mechanism may be associated with cumulative airway damage from the viral and atopic pathways.[16] However, other manifestations of the atopic phenotype, especially excessively Th2-cell-polarised cellular immune responses to the infecting virus in infants at high risk,[63] may also contribute to develop persistent asthma. Developmental deficiencies in the ability of T-helper-1 cells to produce cytokines (eg, interferon γ), which are a feature of infants at high risk of atopy,[64] are also associated with risk for respiratory syncytial virus[65,66] or rhinovirus infection in infancy.[67] Respiratory viral infection markedly upregulates local innate immune functions, especially the activity of airway mucosal dendritic-cell populations,[68,69] which control development and expression of adaptive cell-mediated immunity against the pathogen. These dendritic cells also provide the initial trigger for the CD4+ Th2-cell component of the late-phase response of asthma in atopic patients[37] and, via this route, the viral infection may enhance the immunopathogenic potential of pre-existing inhalant allergy (figure), creating a heterogeneous inflammatory milieu that is associated with greatest risk of asthma development.[9,70]

The role of atopy in asthma on a population basis has been clarified by a recent analysis of the Third National Health and Nutrition Examination Survey (NHANES III),[71] which showed that 56% of asthma cases in the USA were attributable to atopy. This survey included data from people aged between 6 years and 59 years, and suggested that the proportion of asthma attributable to atopy was higher in male than in female individuals (74% *vs* 43%), with further variations related to education and housing status.[71] Initial analyses of 1400 individuals from the 14-year follow-up of the community-based birth cohort from Perth[9] indicated that the proportion of asthma attributable to atopy was 52% overall. However, in contrast to the NHANES III data, atopy accounts for asthma more often in female (66%) than in male individuals (46%). This sex difference may be specific to adolescence, and thus not seen in other age groups. These data come from developed countries and the relation between atopy and asthma may not be the same in populations from developing countries.[13] However, even under conditions where non-atopic asthma is the most common phenotype, atopy is still associated with severe asthma.[13]

Early identification of children at risk of persistent asthma: new clinical indicators

Several attempts have been made to produce models or clinical indicators of risk of persistent asthma at young age.[32,72,73] These models have used asthma risk factors identified in epidemiological studies including: parental

history of asthma and atopy; history of wheeze; presence of other atopic conditions, such as eczema, rhinoconjunctivitis, or food allergy; increased serum concentrations of IgE; and in-vitro cytokine production. Although children identified with these models have a high risk of developing persistent asthma, negative predictive values are higher than positive ones,[32,72,73] indicating that these models are better at excluding asthma than at predicting it, and are thus not suitable for identifying the children at high risk who are likely to benefit from prevention strategies.

Longitudinal follow-up in various birth cohort studies have shown that the best use of atopy indices for assessment of asthma risk can only be achieved in an appropriate clinical context, where these indices need to be assessed against other information, including family history, age, and sex, which is obtained under standardised conditions. This list is expanding with new candidate markers, such as body-mass index,[71] ethnic origin,[71] sleep quantity and quality,[74,75] environmental pollution such as traffic noise and fumes,[76] and genetic markers.[77]

Evidence suggests that quantitative measures of atopy,[27,78–81] especially cumulative titres of IgE specific for perennial inhalant allergens,[82,83] provide more robust assessments of atopy-associated risk than simple binary classifications, such as sensitised or non-sensitised. In a large birth cohort from Perth, Australia,[7] severity of atopy, judged by the number of positive skin-prick tests and wheal size, was related to both the risk of current asthma and severity of asthma at 6 years of age. Linear relations were also seen between serum concentrations of eosinophil cationic protein, a biomarker of eosinophil activation, and skin-prick-test wheal size, and asthma severity.[7] Associations between quantitative measures of atopy and increased risk of asthma, severity of food allergy,[27] and responsiveness to bronchial allergen challenge have been reported in other paediatric cohorts.[79] These findings suggest that the continued use of atopy as a binary variable for assessing asthma risk is not justifiable.

Personal atopic history in early life seems to be one of the key factors to identify an individual's risk of persistent asthma. Recent data from longitudinal cohort studies address the inter-relations between different clinical manifestations of atopy.[27,84] The German Multicentre Allergy Study (MAS)[84] reported a cumulative prevalence of atopic dermatitis in the first 2 years of life of 21·5%. When associated with allergic sensitisation, atopic dermatitis was a good predictor of asthma at school age; the risk was not seen with atopic dermatitis in the absence of sensitisation. However, in many children in this cohort wheeze was seen before or at onset of atopic dermatitis rather than as a progression of atopic disease.

The finding that atopic dermatitis per se does not constitute a risk for asthma, but only when associated with allergic sensitisation, was supported by findings in a cohort of Australian children at high risk.[27] In this study, the risk for asthma was significant (odds ratio [OR] 3·52 [95% CI 1·88–6·59]) at early school age in children with atopic dermatitis and sensitisation to food allergens in the first 2 years of life. The risk was greater with large wheal size predictive of clinical food allergy (4·61 [2 34–9·09]). Also, in this study the risk of asthma did not increase with atopic dermatitis in the absence of allergic sensitisation. These findings and others from cohorts at high risk[85] show that infantile eczema and genuine atopic dermatitis (ie, associated with allergic sensitisation) are not synonymous, and that non-atopic eczema does not convey a risk for asthma. Thus, objective measurement of atopic status, including quantification of markers of sensitisation, is needed to quantify asthma risk. Sensitisation to hens' eggs seems to convey the greatest risk.[27,84] These conclusions come from both high-risk[27,85] and community-based cohorts,[84] suggesting that they are applicable to the general population.

In addition to atopy and respiratory infections, various environmental factors contribute to risk of asthma development through prenatal or postnatal exposures, including environmental tobacco smoke,[86–88] type of bedding,[89,90] indoor and outdoor air pollutants,[91–94] psychosocial factors,[95] and bioaerosols containing microbial breakdown products[36] or allergens.[37] The effects of exposures to these factors may be modified by genetic[96,97] and epigenetic[98,99] factors. In-vitro models suggest that environmental conditions that compromise the barrier function of the airway epithelium could enhance replication of respiratory viruses[100,101] and, consequently, respiratory morbidity. However, the role of some environmental exposures in inducing asthma is not clear. For example, exposure to pets or farm animals is protective in many but not all studies, and controversy still exists about whether prolonged breastfeeding increases the risk of persistent asthma in all children or only in those with atopic mothers.

At present, the identification of a child at high risk might not be possible with absolute certainty. Current research points to some indicators, including family history of asthma and allergies (especially maternal history), early and severe sensitisation to some food antigens (especially hens' eggs) and to aeroallergens, and early viral infection associated with wheeze and adverse environmental exposures. Further comprehensive studies are needed to develop good clinical indicators of high risk.

Potential benefits of early identification of children at high risk of persistent asthma

A substantial proportion of children who develop persistent asthma are not identified until their disease has already consolidated; thus, any potential benefits of early intervention are not achieved. But are these potential benefits real or imagined? One argument supporting the

existence of real benefits is the Hawthorne effect, which is seen in the control group of intervention studies and in observational studies—notably, the improved disease outcomes (relative to the community) that are achieved from simple provision of current best practice care to individuals at risk.[102] We argue that the ability to identify children at risk of developing persistent asthma with a high degree of certainty might enable several important interventions to be undertaken, including: early start of appropriate therapy, which can control asthma symptoms and reduce the burden on the child, the family,[2] and the community;[103] appropriate advice to parents of wheezing children, including advice of allergen avoidance in sensitised children;[104] and specific allergen immunotherapy in children who are most likely to benefit.[6,8] Furthermore, routine advice that should be given by all primary-care physicians and paediatricians to avoid exposing young children to environmental contaminants, such as cigarette smoke, pollutants, and noxious chemicals, could be further strengthened for parents of children at high risk. Ensuring that these children are actively engaged with clinical follow-up may also provide an important benefit.

Intense research is in progress worldwide on various aggressive early intervention strategies,[62] including immunotherapy, immunoprophylaxis, and prevention of lower respiratory infection associated with wheezing with immunomodulatory approaches, antiviral approaches, or both. To test the validity of these strategies, children who are most likely to benefit from early intervention need to be identified. At present, our ability to define the state of high risk is inadequate and needs further research. Nevertheless, early identification and quantification of specific allergic sensitisation, together with accurate assessment of severity and stability of sensitisation, is a logical step in this direction.

Overall, objective assessment of atopy by quantitating allergen-specific IgE in serum against common food allergens (eg, hens' eggs and cows' milk) and local aeroallergens (eg, house dust mite and *Alternaria*) by 2 years of age in conjunction with the presence of other atopic manifestations (eg, atopic dermatitis or clinical food allergy) can help identify the wheezing children who are at high risk of developing persistent asthma. The ability to recognise these children may provide individual benefit by ensuring they are actively engaged with clinical monitoring and providing them with current best practice management. This ability will also facilitate appropriate selection of individuals for clinical trials to assess new prevention strategies.

Contributors

PH and PS had the idea to write this review and wrote the first draft of this review. ALB, BB, AB, AC, PAE, JEG, JG, EH, PJH, RFL, FM, SP, HR, HS, EvM, UW, and PGH were invited to provide comments, which were then incorporated into the final version of this Review. Authors were invited based on their contribution to the literature in this area, especially in relation to major prospective birth cohort studies.

Conflict of interest statement

We declare that we have no conflict of interest.

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