

FOOD ALLERGY AND PRESCHOOL ASTHMA

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ABSTRACT

Asthma is a chronic disease that affects many children worldwide. Atopic march suggests that asthma is preceded by other atopic events such as transient or persistent food allergy and atopic dermatitis. A growing number of large cohort studies has supported a greater appreciation for the heterogeneity of asthma, especially with regard to its diverse aetiologies. It is critical to monitor asthma in food-allergic preschool-aged children. Several studies have begun to reveal connections between food allergy and the eventual development of allergic asthma that appear to verify the atopic march. As the incidence of both food allergy and asthma increases, it is critical to understand the genetic and environmental factors that predispose children to atopic disease, and to understand how early clinical manifestations such as food allergy can increase the risk for chronic allergic diseases such as asthma.

Keywords: food allergy, preschool asthma

INTRODUCTION

Asthma is the most common chronic disease in childhood,¹ affecting approximately 11.6% of children ages 6–7² and up to 15% of preschool-aged children.³ According to the World Health Organisation (WHO), the incidence of asthma continues to increase and is responsible for approximately 250 000 deaths per year.¹ The incidence of food allergy similarly continues to increase.⁴ Beyond its impact on patient health, it significantly reduces quality of life and contributes to financial burdens on patients and health systems. Our current understanding of asthma is that it represents a syndrome that is more complex than a specific mono-causal disease entity.⁵

ENDOTYPES VS PHENOTYPES

Recent efforts have been made to sub-classify further the distinct phenotypes and aetiologies of asthma into ‘endotypes’ defined by unique functional or pathobiological mechanisms. This approach is complicated by the fact that the diagnosis of asthma in preschool age can be very challenging because of the restricted number of validated tests. Accordingly, each distinct endotype responds differently to a variety of treatments. Two endotypes are specifically relevant to preschool-aged children. The first is the ‘Asthma Predictive Index (API)-positive preschool wheezer’: more than three prolonged episodes of wheezing, provided that a major criterion – parental asthma, atopic dermatitis or sensitisation to an aeroallergen – or two

minor criteria – more than 4% peripheral eosinophils, wheezing outside of cold, and sensitisation to a food allergen – are also satisfied. The second is ‘allergic asthma (adults)’.⁶ Although this PRACTALL consensus article describes ‘allergic asthma’ as affecting adults only, the authors also associate it with a history of asthma and eczema in childhood. Therefore, it is relevant to consider allergic disease in the preschool years and its association with adult asthma. Preschool-aged patients with variable presentations, aetiologies and phenotypes of asthma respond variably to current treatments.^{7,8}

A key concept of clinical trajectories in childhood allergic disease is called ‘atopic march’. This sequence of disease phenotypes has traditionally been understood to move from atopic dermatitis (AD) to food allergy, allergic rhinitis (AR) and, ultimately, to persistent allergic asthma. Recent large-scale population studies have revealed a multitude of connections between early childhood atopic disease and more severe allergic disease later in life. These datasets suggested a better response rate to inhaled steroids in cases of Th2 inflammation (eosinophilia, aeroallergen sensitisation).^{7,8} Notably, both the ‘API-positive’ and the ‘allergic asthma’ endotypes are characterised by a Th2 predominance. Therefore, irrespective of the diagnostic and treatment-related limitations present in preschool asthma,⁹ atopy represents a significant risk factor. Children with asthma also commonly suffer from a number of atopic diseases.

BARRIER DYSFUNCTION AND ALLERGIC SENSITISATION

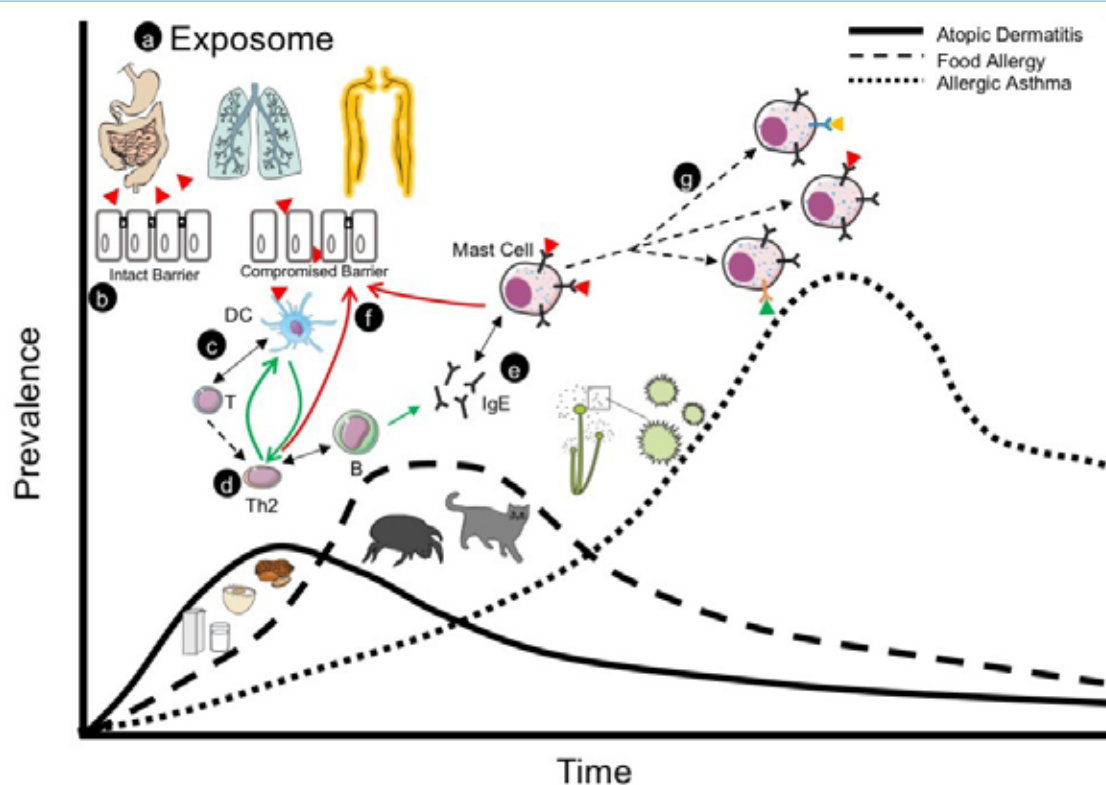
AD is the first disease in the atopic march. The current understanding of AD embraces the fact that skin-barrier defects are instrumental in driving disease and facilitate the high percentage of allergic sensitisations, particularly in patients with severe AD. This predisposition to become sensitised to a number of environmental allergens in the context of an atopic predisposition forms the starting point of the so-called 'atopic march'. Once sensitised to the respective allergen, IgE binds to the high-affinity IgE receptor on the surface of basophils and mast cells in tissues. Subsequent exposure to the allergen triggers the release of mediators that cause an allergic reaction.¹⁰

In line with the barrier-defect hypothesis, consistent exposure of the immune system to environmental allergens via antigen-presenting cells such as dendritic cells or B cells via CD23, the low-affinity IgE receptor, increases the allergen-specific IgE repertoire to different allergen families. It also permits slightly altered antigens with a lower binding affinity to trigger the production of new IgEs. In this way, one allergic epitope can

give rise to a variety of allergies. This phenomenon is known as 'epitope spreading';¹¹ it is a molecular mechanism potentially at the root of atopic march. Therefore, a singular clinical manifestation (AD) spirals into multiple clinical conditions (food allergy, AR, asthma). Biological barriers maintain integrity and regulate the interactions between environmental antigen and the immune system. The skin, the airway epithelium and the gastrointestinal tract are constantly exposed to antigens and allergens, yet not all people develop allergy. Several longitudinal studies have begun to shed light on factors that predispose individuals to atopy, among them a loss-of-function (LOF) mutation in the filaggrin (FLG)^{12,13} gene, which has been linked to allergic disease¹⁴ and AD.^{15,16} Such an association clearly establishes the importance of epithelial barrier integrity and implicates its loss in inflammation.

FOOD ALLERGY AND ASTHMA

Of special concern when considering preschool-asthmatic children and allergic sensitisation is food allergy. Most importantly, children with food allergies who suffer from asthma are particularly at risk of having severe, potentially life-



Allergy to foods such as milk, egg and peanut has been associated with later atopic disease, including allergy to aeroallergens from dust mites, pets and pollen, and with allergic asthma. The exposome includes environmental allergens and antigens (red triangles) that come into contact with biological barriers, including the GI tract, airway epithelium and skin (a). Barrier defects, such as in LOF FLG mutations, can result in a loss of tight junctions, compromising barrier integrity (b). Antigen presenting cells, such as dendritic cells (DC), can pick up and present antigen (c), initiating the differentiation of T lymphocytes into subsets such as Th2.

Th2 cells promote further antigen processing and presentation (d), and stimulate B cells to produce allergen-specific IgE (e), which can then prime the surface of mast cells. Mast cells and Th2 cells further compromise barriers by secreting inflammatory molecules (f). The phenomenon of epitope spreading increases the diversity of IgE on mast cells, which also increases the risk of allergic inflammation at biological barriers (g).

Figure 1: IgE-mediated immune response to allergens and progression of atopic march. (Partially adapted from Servier Medical Art under Creative Commons License CC BY.)

threatening events in response to an allergic reaction.^{17,18} The functional link between loss-of-function (LOF) mutations in FLG and food allergy is not as clear as that in AD; however, patients with the mutation and AD are more prone to developing food allergy. FLG is not expressed in the bronchial airways or in the gastrointestinal tract beyond the oral mucosa,¹⁹ but linkages between primary and secondary barrier dysfunction, on the one hand, and asthma²⁰ and food allergy,²¹ on the other, are established. Therefore, factors other than FLG mutations must also be relevant to barrier function and asthma.¹⁶ The skin as a sensitising organ to food and inhalant allergens has to date been largely under-appreciated, and food allergy and respiratory allergy have not been given due consideration as key steps in the atopic march. In line with this argumentation, the German Multicentre Allergy Study (MAS) reported that sensitisation to egg at the age of 12 months is predictive for sensitisation to airborne indoor and outdoor allergens.²² Another interesting theory suggests that type 2 inflammation has a significant impact on tight junction integrity in the lung and as a result facilitates respiratory sensitisation.^{23,24}

LESSONS FROM COHORT STUDIES

Several large cohort studies support this progression of the atopic march. The MAS study followed more than a thousand participants from 1990 until adulthood and revealed that those with two allergic parents were three times more likely to have allergies than those with two healthy parents. In addition, they found that asthma was more likely to occur with another allergic condition (such as AR or AD) than to occur on its own.²² Significantly, children in the MAS cohort with long-lasting sensitisation to food allergens in the first two years of life had a 3.4-fold higher risk for AR and a 5.5-fold higher risk for asthma when compared to children with only transient sensitisation.²⁵

The Canadian Healthy Infant Longitudinal Development (CHILD) Study was launched in 2008 and recruited 3 500 pregnant women with the aim of better understanding genetic and environmental contributors to atopic disease. It was found that children at three years of age with AD but without allergic sensitisation were not at increased risk of food allergy and were also not at increased risk of asthma. Children with both AD and allergic sensitisation were found to have seven times the risk of developing asthma. Importantly, food sensitisation was found to be more responsible for this effect than environmental allergen sensitisation, and increased risk occurred even with no AD.²⁶

Similar findings were reported by Alduraywish et al, who investigated two birth cohorts (MACS and LISAPlus). The sensitisation to food at ages 6, 12 and 24 months resulted in a significantly higher risk of developing asthma at the age of 10–12 years. This risk was further increased if children displayed co-sensitisation with aeroallergens.^{27,28}

In the HealthNuts cohort from Melbourne, asthma, eczema and food allergy were assessed at 12 months and four years of age. Approximately 11% of children at 12 months had a food allergy, but by age four only 3.8% had food allergy.²¹ Subsequent analysis of the dataset revealed that children with one food allergy confirmed by oral challenge at 12 months were 1.69 times as likely to have asthma than those with no food allergy; those with two or more food allergies were 2.76 times as likely to have asthma.²⁹ Asthma risk was further increased by eczema and by persistent rather than transient food allergy, at least in the case of egg. This cohort in particular draws a clear connection between food allergy, eczema and risk for asthma.

The CDC has reported that asthma affects 4.7% of children aged 0–4 years and affects 9.8% of children aged 5–14 years.³⁰ They have also reported that 4.7% of 0–5-year-old children have food allergy, whereas 3.7% of 5–17-year-old children have food allergy.³¹ Examining the connection between the two variables is difficult as there is no gold-standard test for asthma, given its diverse endotypes; moreover, the gold-standard test for food allergy – a double-blind placebo-controlled food challenge – is time-consuming and the data are impractical to collect on the scale of a cohort study.

However, serological data from the National Health and Nutrition Examination Survey (NHANES) cohort suggests that of those with diagnosed asthma 27.5% have a food sensitisation and, of those, 1.9% have 'likely food allergy'; conversely, of those without asthma, 14.9% have a food sensitisation and, of those, only 0.9% have 'likely food allergy'.³²

CLINICAL IMPLICATIONS

This significant body of evidence linking sensitisation to food allergens, which is a surrogate marker of food allergy, implies that children with polysensitisations early in life are at high risk of developing persistent asthma. In addition, AD has been identified as an independent risk factor that contributes significantly to asthma risk. As such, these patients may be identified, and their parents may be informed about that risk and followed up with in order to guarantee a timely and accurate diagnosis and treatment of asthma. Moreover, food allergens should also be considered as a potential trigger factor of severe intermittent asthma in the absence of environmental triggers.

CONCLUSIONS

Food allergy is a significant co-morbidity of preschool asthma and vice versa. The management of preschool asthma may significantly improve upon characterisation of its underlying mechanisms. This will allow risk factors to be elucidated for discrete asthma endotypes linked to severe anaphylaxis in asthmatic patients and could result in novel preventive and therapeutic concepts of allergic diseases such as AD, asthma and food allergy.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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