

EDITORIAL

Clinical & Experimental Allergy

The role of food allergy in the atopic march

This editorial discusses the findings of the paper in this issue by Malmberg et al. [11] pp. 1491–1497.

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The rise in allergic diseases including asthma, eczema and allergic rhinitis (AR) over the last 30–40 years has been well described using large-scale population-based studies [1]. By contrast, IgE-mediated food allergy, which also occurs in those with an atopic predisposition, has not been systematically studied in population cohorts until recently, presumably because it is less common than the other three manifestations. Recent studies showing a significant increase in the last 10 years of food allergy-related hospitalizations for anaphylaxis [2, 3], the most severe manifestation of food allergy, lend credence to the idea that there is also a rise in food allergy in general and that this may form a 'second epidemic' of allergic disease [4]. Certainly, burgeoning clinical waiting lists in Australia, Europe and the United States with children presenting with easily identifiable acute allergic IgE-mediated reactions to food (including urticaria, angioedema, vomiting or anaphylaxis) suggest that the rise is not simply due to an over-reaction by the public to media reports of the devastating but extremely rare sudden death of a healthy child with food allergy-related anaphylaxis.

To date, the majority of population cohorts investigating allergy have utilized IgE testing to food allergens (either through skin prick test or serum levels) as a surrogate marker of food allergy. Unfortunately, these measures are inexact as they overestimate food allergy status with up to 50% of sensitized children orally tolerant to that particular food allergen. Challenge-based confirmation of food allergy, either as an open food challenge under observation in young infants or as a double-blind placebo-controlled food chal-

lenge in older children and adults, remains the gold standard for identifying food allergy. However, formal food challenges are time consuming and often therefore prohibitively expensive and until recently have not been utilized in large population-based studies. This has resulted in a dearth of accurate estimates of food allergy prevalence and potentially affected the ability to identify risk associations due to misclassification of food allergy outcome data. Because of the concern that IgE-mediated food allergy is on the rise, a number of cohort studies have now been mounted to assess the prevalence of food allergy using the more accurate measure of food challenge confirmation with the secondary aim of describing environmental and genetic risk factors that may predispose children to food allergy [5, 6].

A further vexing issue in this field of research is whether the apparent increase in food allergy represents a discrete and independent predictor of a subsequent increase in other allergic manifestations. That is to say – are children with IgE-mediated food allergy also at an increased risk of the 'atopic march'? The 'atopic march' is described as the progression from early-onset eczema to asthma and AR later in childhood and into adulthood [7, 8]. The term was originally coined to describe the sequential manifestation of atopic disorders, although it is not yet known whether the progression from one allergic outcome to another is causal or a result of shared environment and/or shared genetics [9]. New population-based prospective cohort studies that incorporate food allergy as a baseline outcome are now needed to reasonably assess the role that food allergy plays in predisposition to incident and/or persistent asthma.

By contrast to food allergy, asthma research remains hamstrung by the absence of gold standard objective markers for the diagnosis of asthma, particularly between episodes of exacerbation. There is growing evidence that there are many subgroups of asthma with many pathological mechanisms that cause airway inflammation, the

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hallmark of asthma. For example, some people with asthma have eosinophilic inflammation, some have neutrophilic inflammation and some may have no influx of inflammatory cells [10]. Furthermore, there is an ongoing debate about whether non-atopic asthma represents a disease outcome related to different causal factors to those of atopic asthma. Hence, it is important to investigate the relationship between food allergy and different phenotypes of asthma when investigating the role of food allergy in the atopic march.

The article in this issue of *Clinical & Experimental Allergy* by Malmberg et al. [11] is the first to formally and prospectively assess whether challenge-proven cow's milk allergy in infancy predisposes children to bronchial hyperresponsiveness and airway inflammation (rather than just self-report) as a surrogate marker for asthma at school age. As such, the authors are attempting to unravel the question as to whether those who have food allergies are at an increased risk of progressing through the atopic march. This is an important association to investigate as the identification of a high-risk cohort of allergic children early in life might provide a suitable window of opportunity for therapeutic intervention to prevent progression from food allergy to asthma, the latter of which presents a significant burden of disease to the adult population.

The authors prospectively followed 118 (1.9%) children with cow's milk allergy at baseline who were originally part of a population-based birth cohort of 6209 full-term infants recruited in 1994/1995. The authors have already reported that IgE-mediated CMA often persists to school age and is a risk factor for other atopic disease such as asthma, rhinoconjunctivitis and eczema, while non-IgE-mediated CMA, by contrast, is a benign infantile condition [12]. The current manuscript presents the results of the association between different types of cow's milk allergies and signs of airway inflammation as defined by higher exhaled nitric oxide (F_{ENO}) and an increased bronchial responsiveness to histamine as an indirect objective measure of current asthma. The authors found that children with IgE-mediated cow's milk allergy diagnosed at a mean age of 7 months were more likely to have both an increased F_{ENO} and BHR at the age of 8 years than either those who did not have food allergy or those with non-IgE-mediated cow's milk allergy. These associations remained significant after adjustment for some potential confounders. History of wheeze in the first year of life and parental smoking were also factors independently associated with the increased F_{ENO} and BHR at school age.

A major strength of the study is the use of an unselected birth cohort and a good follow-up retention rate, although it should be noted that the baseline participation rate of the study was only 40% and there is likely to be a degree of self-selection bias towards higher participation by children from families with a family history of allergy. This cohort is also one of the few to use challenge-proven

food allergy outcomes. However, the study is relatively underpowered for the less common outcome of IgE-mediated food allergy and therefore is limited in its ability to adjust for all important confounders simultaneously. Because of the low power, the authors are also unable to formally undertake an incidence analysis to delineate whether the observed association is related to co-manifestation of other allergic conditions such as eczema and AR that predict asthma or is a consequence of CMA itself.

A further strength of the study is that the authors have explored the relationship of baseline food allergy status to the development of different markers of asthma. In this publication, they have considered the outcome of BHR and F_{ENO} and self-reported asthma in their previous publication. Childhood BHR and F_{ENO} are considered as indirect objective markers of airway inflammation, which is a hallmark of asthma. However, as the authors themselves point out, BHR and F_{ENO} reflect current inflammation and poorly controlled asthma and are not a true surrogate for the diagnosis of asthma. It is known that these markers can occur without any symptoms of asthma and asthma can occur without any of these markers. On the other hand, asymptomatic airways inflammation has been observed in childhood asthma some years before clinical presentation and therefore may be one of the earliest manifestations of asthma [13]. As such, the level of airway inflammation may not only reflect the current state of the airways but also as evolving evidence suggests it may predict the development as well as persistence of childhood asthma [14].

When the overall results of the 8-year follow-up of this cohort are taken together, they provide emerging evidence that challenge-proven CMA is likely to be one of the earliest steps in the atopic march towards airway inflammation and asthma. However, larger population-based cohorts are urgently needed in order to explore further whether food allergy truly represents an earlier manifestation of the atopic march with shared environmental and genetic determinants or whether it is an independent predictor. Continuation of methodologically rigorous population-based studies with either a high prevalence of challenge-proven food allergy or larger cohorts for those regions with a lower prevalence of food allergy will provide the appropriate power to address these pressing questions in the coming years. In the meantime, the search for modifiable environmental and lifestyle factors that might be driving the development of allergic diseases in the last several decades remains critically important and hopefully eminently achievable.

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