Asthma and Food Allergies

EDITOR'S PICK

The relationship between food allergy and asthma is already well known. This review article looks at this relationship and suggests early intervention strategies in clinical practice. It is important to establish the presence of allergy early by appropriate testing and to start treatment, because the clinical implications for children with both diseases could be significant.

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Abstract

There is a close association between various atopic diseases and it is well known that having one atopic disease can increase the risk of further atopy later in life. Research has shown that the development of food allergy in infancy can predispose individuals to the development of respiratory symptoms and subsequent asthma later in childhood. There is also evidence that shows early atopic conditions can be outgrown but may still influence the development of other atopic conditions, such as asthma, in the future. The exact mechanism of how this occurs is not yet fully understood, but the clinical implications for children with both diseases are important because not only are they at greater risk of more severe asthmatic episodes, but also of having respiratory symptoms in food-induced anaphylaxis. This narrative review looks at the relationship between food allergy and asthma and how they are linked to one another. It will also focus on the clinical implications associated with the two atopic conditions and the effect they may have on clinical practice.

BACKGROUND

There is a long-established link between allergic diseases in atopic individuals, whereby having one atopic condition can predispose that individual to others. These diseases include asthma, allergic rhinitis or hayfever, eczema, and food allergies, and they are increasingly common in the paediatric population. There are a multitude of contributing factors, including genetic and environmental, with research providing supportive evidence that there are genes that predispose individuals to atopic conditions.[1,2] A recent systematic review of sibling and twin data found that genetics played a bigger role in predisposing eczema patients to both hayfever and asthma compared to environmental factors, but the link between these atopic conditions was independent of shared early-life environmental factors.[2]

The natural progression in the development of atopy is often referred to as the 'atopic march'.[2,3] The most common pathway along the atopic march is for children to develop eczema during infancy and then, as they get older, they may develop food allergies, followed by allergic rhinitis and asthma. Allergic sensitisation to food early in life has been shown to be associated with the later development of respiratory symptoms and/or asthma. This review article looks more closely at this link between food allergy and asthma.

FOOD ALLERGY

The prevalence of food allergy has increased over the last 20 years,[4,5] which has also led to increased research into food allergies in children. Depending on the country, approximately 4–10% of children have food allergies, which usually develop early in life.[6-8] A food allergy is defined as an adverse immunological reaction that occurs upon exposure to a food and is reproducible following repeat exposure.[9] These immunological reactions are classified as immunoglobulin E (IgE) or non-IgE depending on the clinical history of presenting symptoms and the results of the investigations, such as skin prick tests, specific IgE levels in the blood, and oral food challenges. Food allergies often present during infancy; in fact, research has shown that in some locations >10% of children aged 1 year old have a food allergy.[10] Common foods that children are allergic to include eggs, cow's milk, wheat, and peanuts.[8] There are various routes by which allergen exposure can occur; for example, it can occur orally via the gastrointestinal tract, cutaneously via the skin barrier, or via inhalation through the respiratory tract. Allergy develops following exposure of an allergen to the immune system, namely antigen-presenting cells that engulf the allergen and activate naïve CD4 T-helper lymphocytes, which results in the production of antigen-specific antibodies to the allergen by mature B cells. These antibodies bind to mast cell surface receptors in various tissues of the body, as well as to cell-surface receptors on basophils in the bloodstream. Thus, on repeat exposure, the allergen binds and crosslinks these specific IgE antibodies triggering degranulation and release of inflammatory mediators, thus causing an allergic reaction.[11] IgE-mediated allergic reactions to food have a rapid onset after exposure to the allergen (usually <2 hours) and can present with various symptoms, such as respiratory (wheeze, shortness of breath, difficulty in breathing), gastrointestinal (vomiting, diarrhoea), and skin (urticaria, rash), or, if severe, anaphylaxis. Lower respiratory symptoms are commonly seen in food-allergic reactions in asthma patients, although asthma is rarely seen as the sole manifestation of food allergy presentations.[12] Non-IgE-mediated food allergy has a slower onset of symptoms, which can be chronic in nature due to ongoing allergen exposure and can occur if the association between the allergen and the symptoms is not recognised. Symptoms of non-IgE-mediated allergy mimic many common childhood conditions, such as eczema, gastro-oesophageal reflux, and constipation, but can also present with chronic mucousy stools.

Children with food allergies are at risk of developing other allergic conditions, but there are little data available on long-term outcomes of food allergy in infancy and childhood in terms of the future development of other allergic conditions. A recent study by Peters et al.[13] found that 40–50% of the children diagnosed with challenge-confirmed food allergy at 1 year of age had symptoms of an allergic disease, such as wheeze, itchy rash, and/or nose symptoms, in the first 4 years of their life.

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ASTHMA

Asthma is a chronic disease affecting approximately 9% of children around the world and is characterised by inflammation of the airways and bronchial hyper-reactivity causing recurrent symptoms of cough, wheeze, shortness of breath, and difficulty breathing.[2,14] The pathophysiology in acute episodes of airway narrowing is the result of a combination of factors, including an increase in populations of inflammatory cells (i.e., mast cells, eosinophils, macrophages, lymphocytes, dendritic cells), which, when triggered, produce mediators that result in airway hyper-responsiveness and narrowing.[15] However, with recurrent episodes and disease progression, airway changes can continue to progress and eventually result in airway remodelling, such as increased smooth muscle, thickening of the basement membrane, and a loss of normal distensibility of the airway.[15] Traditionally, there has been a focus on controlling the inflammation with inhaled corticosteroids and relieving the bronchial constriction with bronchodilators such as salbutamol. This occurs in conjunction with anticipation of the impact of physical triggers such as exercise, pollution, and cold air. While this is still important, there is an increasing recognition that there may be an allergic component in the development of asthma with aeroallergens (i.e., house dust mite, cat and dog dander, grass and tree pollens) being predominant triggers. These children often have positive skin prick tests and/or specific IgE blood tests to the common allergens, which makes it relatively straightforward to identify the triggers and, in some cases, make efforts to try and avoid them.[16] There have also been studies that show that children as young as 6 months of age with high levels of IgE and reactivity to aeroallergens have an increased risk of developing asthma.[17,18]

Various atopic phenotypes have been reported in the literature that describe how the presence of different risk factors (i.e., sensitisation to specific allergens) are linked to the risk of asthma progression.[19] The phenotypes include sensitisation based on type of allergen (e.g., dust mite compared to non-dust mite) or early or late sensitisation.[19] One study found that the risk of new-onset bronchial hyper-responsiveness was highest in children who had early sensitisation to outdoor allergens (including *Alternaria* mould) and later sensitisation to indoor allergens (including *Aspergillus* mould).[20] Other studies have looked at sensitisation in birth cohorts to various allergens, and these studies resulted in the finding that the development of asthma at 6 years of age was associated with earlier sensitisation to dog and cat allergens.[21,22]

There is also evidence to suggest that aerosolised food proteins can induce food-triggered asthmatic episodes as the inhalation of allergenic food proteins stimulates an inflammatory reaction of the mast cells in the airways causing wheeze and shortness of breath.[14] Occupational asthma has been described extensively in adults because of chronic inhalation of food allergens in a work environment. The wheeze of a baker with asthma occurs due to inhaled flour proteins triggering a localised IgE-mediated reaction.[23] Chronic exposure to aerosolised fish can cause the same problem and these aerosolised proteins have been detected in fish markets.[24] In a study of a paediatric cohort with proven IgE-mediated food allergy and asthma, the researchers found that even with dietary avoidance of the food the children were allergic to (i.e., fish, milk, eggs, chickpeas, buckwheat), if the families continued to cook the allergenic food in the home environment, the children's asthma symptoms were worsened due to environmental exposure to the food. However, if the families stopped cooking the allergenic foods in the home environment, there was a reduction in the child's asthma symptoms and also in their need for inhaled corticosteroid treatment.[25]

There have also been studies that have looked at respiratory symptoms as a result of exposure to airborne food particles on flights.[26] In a study on adults who self-reported an allergic reaction to peanuts, tree nuts, or seeds during a flight, 9% reported a reaction on planes, with the most commonly reported mode of exposure being inhalation of airborne particles.[26,27] However, in a study of children with severe or reported inhalational reactions to peanut who had blind inhalational peanut challenges (i.e., peanut butter was held 12 inches from the face for 10 minutes), they did not exhibit any allergic symptoms.[28] Furthermore, a study conducted by Brough et al.[29] looked at the distribution of

peanut protein in the home environment by measuring airborne peanut protein levels in a number of simulated scenarios and found that peanut protein was unlikely to be transferred into the environment by aerosolisation.

THE LINK BETWEEN ASTHMA AND FOOD ALLERGY

Food allergy and asthma are known to coexist, but the extent to which they may impact one another is still not fully established. Approximately half of children with food allergies have reactions that involve respiratory symptoms[30] and of children who have asthma, 4–8% have food allergy.[31]

There is indirect evidence that food allergic infants have an increased risk of developing asthma later in life.[32-34] Illi et al.[35] found that a strong predictor of asthma development by school age was food sensitisation early in life (i.e., before 2 years of age) either with or without concurrent inhalant sensitisation. Another recent large retrospective birth cohort study showed that food allergy was associated with the development of asthma and rhinitis, and rates were approximately double in those children with food allergies compared to children in the general population.[36] More specifically, the researchers found that the children with allergies to peanuts, milk, and eggs, as well as those with multiple food allergies, had a significant increased risk of developing respiratory allergy (i.e., rhinitis and/or asthma).

Studies have been performed that looked at specific foods and their potential link to asthma. Priftis et al.[34] found that children who were allergic to egg or fish in infancy were at a greater risk of having wheeze and hyper-reactive airways at school age. A study of a Danish birth cohort of 562 children resulted in the finding that both transient and persistent early-life sensitisation to egg was associated with asthma and rhinoconjunctivitis at 14 years of age.[37] This was also supported by evidence from an Isle of Wight birth cohort study[38] that showed egg allergy in infancy was associated with the development of respiratory symptoms and aeroallergen sensitisation by 4 years of age. Furthermore, the authors reported a positive predictive value for asthma of 40% if the child had an egg allergy.[38] Another study by Rhodes et al.[39] found that for infants at a higher risk of developing atopic disease due to a parental family history of atopy, sensitisation to egg and milk in the first year of life was a predictive feature of developing asthma in adulthood.

Research looking at allergen molecules through microarrays provides supporting evidence that sensitisation to allergen molecules (both food and aeroallergens) in early childhood can precede asthma and rhinitis in adolescence.[40,41] More recently, Vermeulen et al.[42] conducted a population-based study that showed children with oral challenge-proven food allergy in infancy have an increased risk of asthma at 4 years of age irrespective of whether their food allergy resolves. They reported that children with ≥2 food allergies and coexistent eczema were also three-times more likely to develop asthma compared to children without food allergies.

MORBIDITY AND MORTALITY

The impact of this link between asthma and food allergy in terms of morbidity and mortality has also been researched, with asthma being a risk factor for fatal or near-fatal anaphylaxis to foods.[12] In a study of asthmatic adults, those who also had an allergy to >1 food were found to have a higher risk of lifetime hospitalisations and visits to the emergency department for asthma as well as increased use of oral corticosteroids.[43] In a study conducted by Simpson et al.[44] including children aged 3 months to 14 years old, those who had milk and peanut allergies had a significantly increased number of hospitalisations due to asthma. Other studies have been performed looking at patients with near-fatal asthma (i.e., requiring ventilation in an intensive care unit) and have found that they were more likely to have a food allergy and/or have had anaphylaxis.[45] Roberts and Lack[31] performed a study that recruited children aged between 1 and 16 years old who had been ventilated for an acute asthma exacerbation in paediatric intensive care and compared these children to matched controls. The researchers found that food allergy was an independent risk factor for life-threatening asthma. It is likely that asthma is a risk factor for anaphylaxis and may be

associated with poorer outcomes for children with food allergy. A study found that children with cow's milk allergy had a 10-fold greater risk of a severe reaction if they also had asthma.[46] More specifically, with regard to actual fatalities, in a cohort of children with peanut allergy, 9% (4/46) of the children died of asthma exacerbation.[47,48] Bock et al.[47] also performed a series looking at food-related anaphylactic fatalities and reported that the majority of the children had a diagnosis of asthma and, for the most severe reactions, respiratory symptoms were most predominant.

CLINICAL IMPLICATIONS AND THE EFFECT ON PRACTICE

This close relationship between asthma and food allergies has, therefore, influenced the way in which clinicians approach children with atopy. As in any consultation, clinical history becomes vital in managing these children, especially if there is a clear account of food exposure causing respiratory symptoms in a child diagnosed with asthma. Alongside this, the use of skin prick testing and specific food and aeroallergen IgE-testing may be useful to confirm allergies and identify triggers. The diagnosis of asthma can be complicated because various asthma phenotypes exist;[49] however, chronic asthma is largely managed with the use of inhaled short and long-acting beta agonists, inhaled corticosteroids, leukotriene receptor antagonists, and systemic corticosteroids. This takes place alongside regular assessment of symptoms, lung function tests if appropriate, and regular reviews for adherence and compliance to treatment.[50]

If an immediate food allergy is identified, the advice is to avoid the allergen. Patients should be equipped with personalised emergency action plans, which should include the administration of an adrenaline autoinjector in the presence of any signs of anaphylaxis (airway, respiratory, or cardiovascular compromise) in patients with both food allergy and asthma or in those patients who have previously experienced anaphylaxis to any food allergen.[51,52] The use of antihistamines in accidental exposure is advised for mild-to-moderate reactions. In an acute emergency presentation of what appears to be life-threatening asthma, in children with both asthma and food allergies, it is also important that the diagnosis of anaphylaxis is considered along with the use of intramuscular adrenaline (in conjunction with ongoing medical management of the presentation of an acute exacerbation of asthma). In most circumstances of anaphylaxis there will also be other features of an immediate allergic reaction, such as cutaneous signs that will guide the use of adrenaline if a history of allergen exposure was not forthcoming.

FUTURE IMPLICATIONS AND AREAS OF RESEARCH

There has been increasing research on the use of immunomodulators in the treatment of allergic diseases, such as the use of monoclonal antibodies. Omalizumab is a monoclonal antibody that selectively binds IgE and has been used in the treatment of allergic asthma.[53] With regard to asthma, omalizumab has been shown to help reduce exacerbation rates, the number of hospitalisations and missed school days, daily rescue medication use, and symptom days.[54] It has also been used in conjunction with allergen immunotherapy, as well as for the treatment of food allergies (i.e., milk, peanut, and egg) in the research setting, with studies showing it may be able to aid in desensitisation to allergic foods but also decrease basophil activation.[55-57] Further research into the therapeutic role of immunomodulators in children with both food allergy and asthma is required to better evaluate the safety of use but also the long-term maintenance of tolerance.

CONCLUSION

There is increasing evidence to suggest that food allergies and asthma in children are linked. Children who develop food allergies are at greater risk of developing asthma, and even those infants who outgrow their allergies may have respiratory symptoms that persist and develop into asthma.[13,42] Those that have both atopic conditions are at increased risk of severe asthmatic episodes, allergen-triggered asthma episodes, and food-induced anaphylaxis. Therefore, clinicians need to be mindful of this associated link in acute presentations of asthma exacerbations or food-induced anaphylaxis to ensure appropriate treatment is delivered.

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