

Atopic march, food allergy and food hypersensitivity in children and adolescents suffering from atopic dermatitis

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Increases in allergic diseases have been well documented worldwide. Approximately one-third of children with severe atopic dermatitis (AD) were reported to suffer from IgE-mediated food allergy as well. Data sources concerning the food allergy, AD, and atopic march were accessed from Pubmed/MEDLINE. This review provides a summary of findings concerning the food allergy, food hypersensitivity reactions, and atopic march in children and adolescents. Food allergy that developed at a young age increased the risk for AD, asthma bronchiale, and allergic rhinitis; new research identifies the skin barrier as not only an important initiator of AD but it may even be a site for allergic sensitization to protein antigens. Early childhood is thought to be a key period for the prevention of allergic march and adolescence is another key period for the prevention of recurrence. The prevention of recurrence would decrease allergic disease in adulthood.

Keywords: atopic dermatitis; food allergy; food hypersensitivity; atopic march

Introduction

Increases in allergic diseases, including atopic dermatitis (AD), bronchial asthma, and allergic rhinitis over the last 30–40 years has been well documented worldwide; studies from diverse industrialized regions of the world reveal an increasing prevalence of their clinical manifestations (Asher et al., 2006; Werfel et al., 2007). Prevalence of these diseases has increased by two to three-folds during the past three decades in industrialized countries. It remains much lower in agricultural regions such as China, Eastern Europe, and rural Africa. Moreover, higher prevalences have been recorded in urban regions than in rural regions of developed countries and the disease is more common in higher social class groups (Larsen & Hanifin, 2002).

Atopic dermatitis and food reactions

Atopic dermatitis is one of the earliest manifestations of atopy with the highest incidence during the first three months of life and constitutes, together with allergic rhinitis and asthma bronchiale, the triad of atopic diseases (Asher et al., 2006). The prevalence of AD is about 10–20% in children and 1–3% in adults (Larsen & Hanifin, 2002; Werfel, Schwerk, Hansen, & Kapp, 2014). In 45% of children the onset of AD occurs during the first 6 months of life, in 60% of children during the first year of life in, and before the age

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of 5 years in at least 85% of affected individuals (Kay, Gawkrödger, Mortimer, & Jaron, 1994).

In those children with the onset before the age of 2 years, 20% have persisting manifestations of the disease and an additional 17% have intermittent symptoms by the age of 7 years. According to Yates, AD is one of the earliest clinical manifestations of allergic disease, with the highest incidence during the first 3 months of life (Yates, Kerr, & Mackie, 1983). In adults with AD, only 16.8% had an onset after adolescence (Williams & Strachan, 1998).

The pathogenesis of AD involves interactions among multiple factors including susceptibility genes, environmental factors such as food and inhalant allergens, skin barrier defects, and immunologic factors (Boguniewicz & Leung, 2010; Leung & Bieber, 2003).

Foods can lead to the worsening of AD in different patterns described as food hypersensitivity reactions. It represents the umbrella term for (1) food allergy and for (2) food intolerance (= non-allergic food hypersensitivity). The term food allergy is used to describe the clinical symptoms that are mediated by the immune system, while the *food intolerance* is a non-allergic hypersensitivity to *food* that does not include the immune system even though the symptoms are similar to those of IgE-mediated allergic *reactions* (Bindslev-Jensen et al., 2004; Li et al., 2001).

Food allergy in children and adolescents

The early onset of AD was found to be associated with high-risk IgE levels in food allergy (Östblom, Lilja, Pershagen, van Hage, & Wickman, 2008; Penard-Morand et al., 2005). Atopic dermatitis starts with chronic skin inflammation after a postnatal preclinical phase (phase 0), but without any evidence for IgE sensitization (phase I). This phase is followed by the emergence of sensitization usually toward food allergen and other environmental factors leading to the classical IgE-associated AD phenotype (phase II). The spreading and chronic inflammation of the skin and the *Staphylococcus aureus* colonization play the important role. A substantial proportion of these patients seems to have a high risk of developing allergic rhinitis and asthma which is further triggered by the chronic skin inflammation and scratching to become sensitized to self-proteins ultimately leading to a kind of autoimmune form of AD (phase III) (Valenta, Mittermann, Werfel, Garn & Renz, 2009; Tang, Bieber & Williams, 2012). About 35% of children with moderate to severe AD have IgE mediated food allergy and about 6%–8% of asthmatic children have food-induced wheezing (Hauk, 2008). But 80% of them outgrow their food allergy. In adult patients with AD, studies investigating the co-prevalence of AD and food allergy are still scarce and exact data are not available (Heratizadeh, Wichmann, & Werfel, 2011; Werfel & Breuer, 2004). The results of a population-based study in Germany involving 1739 unselected patients who had completed questionnaires confirmed that food allergy in adult AD patients is rare (Worm et al., 2006). According to other studies, food allergy appears to be an important factor in exacerbation of AD in only a subset of children (and a much smaller subset of adults). Non-IgE-mediated mechanisms are sometimes implicated in the AD flare-ups associated with ingestion of the foods in question, and food allergy appears to have little or no role in children with nonAD (Rancé, Boguniewicz, & Lau, 2008; Rancé, 2008). According to a questionnaire survey of schoolchildren's perceptions dealt with factors influencing AD, an extremely small proportion (8%) of AD respondents

believed certain foods or drinks have an effect on their disease (Williams, Burr, & Williams, 2004). A survey of adults in High Wycombe showed that 20% perceived adverse reactions to specific food, but only 1% had confirmed food allergies (Host, 1995). According to Sicherer, both AD and food allergy are, in the majority of individuals, transitory conditions that improve with increasing age (Sicherer & Sampson, 1999).

Examinations in suspicion for food allergy

In patients with suspected food allergy, which is thought to be aggravating eczematous lesions, it is therefore important that any food avoidance measures suggested are based on a detailed history and supportive evidence from objective allergy tests. The key here is the role of skin prick testing and measure of specific IgE. Patch tests are recommended in patients with a suspicion of delayed cell-mediated hypersensitivity reactions (Fox, Du Toit, Lang, & Lack, 2004). In cases of diagnostic doubt, oral food challenge may be performed. In this provocation test, early clinical responses are those reactions observed within 2 hours after the last administered dose, late-phase reactions are those occurring between 2 and 48 hours. Food challenges can cause three different patterns of clinical reactions to foods in patients with AD (Werfel et al., 2007): (1) Noneczematous reactions – immediate reactions; the clinical symptoms include cutaneous symptoms such as pruritus, urticaria, and rash and/or noncutaneous gastrointestinal or respiratory symptoms or even anaphylaxis. (2) Isolated eczematous reactions – late reactions, e.g. flare-up after hours to days. (3) A combination of noneczematous and eczematous reactions. In some previous publications, the eczematous reactions were defined as late (i.e. by time) or delayed (i.e. by mechanism) reactions (Heratizadeh, Wichmann, & Werfel, 2011). In order to distinguish eczematous responses clearly from early cutaneous reactions, the food should be given over a period of 2 days. This provocation scheme was recommended for the detection of “true” eczematous late-phase reactions by the German Society of Allergology and Clinical Immunology (Werfel, Fuchs, & Reese, 2002). The skin must be scored by an established eczema score (SCORAD) before the challenge test and at least after 24 hours (European Task Force on Atopic Dermatitis, 1993). It is not sufficient to score eczema just before and immediately after challenge test since eczematous reaction will be missed in many cases. A difference of at least 10 SCORAD points is usually considered a positive reaction (European Task Force on Atopic Dermatitis, 1993). Challenge test should always be performed by persons experienced in challenge test and emergency equipment must be available at all times.

Food allergens

Food allergy is caused by cow's milk, hen's egg, soy, wheat, fish, peanuts, or tree nuts in about 90% of the cases (Suh, 2010). Regarding the course of food allergy, it is well known that about 50% to 80% of children with allergy to milk or hen's egg develop tolerance by school age (Kjaer, Eller, Andersen, Høst, & Bindslev-Jensen, 2009). Allergies to seafood, peanuts, and nuts are more likely to persist (Lack, 2008). Food allergy may be the result of a failure to develop tolerance or the loss of preexisting tolerance. Preliminary results indicate that defects in the epidermal and the gut barrier function may facilitate sensitization to allergens through epicutaneous and gastrointestinal

exposure. Among adults, allergies to cow's milk, wheat, and hen's egg are rare, although exact data are not available. Overall, the body of literature on the association between food allergy and AD in adults is small. Population-based studies show a significantly higher risk of food sensitization in AD patients compared with healthy controls and up to 10% of adults with food allergy have concomitant AD. However, food hypersensitivity reported by patients is often not confirmed by formal challenges (Manam, Tsakok, Till, & Flohr, 2014). According to our results, challenge-proven food allergy was rare (wheat 2.2%, egg 5%, and cow's milk 1%) whereas 11.2% showed allergic sensitization to wheat, 20% to egg, and 10% to cow's milk. (Celakovská & Bukac, 2015; Celakovská, Ettlerova, Ettler, & Vaneckova, 2011).

Aside from allergies persisting since childhood, in Northern and Central Europe, allergies to birch pollen-related foods (hazelnut, carrot, celery, apple) are more common. However, birch pollen-associated food allergy also may be clinically relevant in younger children, especially in children with severe AD and a high sensitization level to birch pollen (Breuer et al., 2004). Peanut allergy represents an increasing problem, involving approximately one in 150–200 subjects. The mean age at detection is decreasing and also 2- to 3-year-old children are affected. A typical at-risk subject is an atopic individual with heightened risk for those with AD and/or other food allergies (Sicherer, 2002). Tomatoes are often mentioned as a cause of oral allergy syndrome and pruritus. There is an increasing consumption of tomatoes worldwide: fresh in salads, cooked in household sauces, or industrially processed. Although many tomato allergens have been identified, there is no information in the literature on the allergenic components found in commercial tomato products. In fresh tomato, different lipid transfer proteins (LTP) isoforms are present and allergenic. Industrial tomato derivatives still contain LTP, thus presenting a problem for LTP allergic patients (Pravettoni et al., 2009). Fruits (in particular acidic fruits such as kiwi, oranges, or lemons) are frequently mentioned as causing symptoms of oral allergy syndrome, pruritus, worsening of AD, or causing gastrointestinal reaction. In patients allergic to fruit, multiple sensitizations to other vegetable products, whether from the same family or taxonomically unrelated, are frequent, although they do not always share the same clinical expression. Furthermore, more than 75% of these patients are allergic to pollen, the type of pollen varying in relation to the aerobiology of the area. The basis of these associations among vegetable foods and with pollens lies in the existence of IgE antibodies against “panallergens,” which determines cross-reactivity. Panallergens are proteins that are spread throughout the vegetable kingdom and are implicated in important biological functions (generally defense) and consequently their sequences and structures are highly conserved. The three best-known groups are allergens homologous to Bet v 1, profilins, and LTP. Allergens homologous to Bet v 1 (major birch pollen allergen) constitute a group of defense proteins (PR-10), with a molecular weight of 17 kDa, which behave as major allergens in patients from Northern and Central Europe with allergy to vegetables associated with birch pollen allergy. In these patients, the primary sensitization seems to be produced through the inhalation route on exposure to birch pollen. The symptomatology characteristically associated with sensitization to this family of allergens is oral allergy syndrome. Profilins are highly conserved proteins in eukaryotic organisms and are present in pollen and a wide variety of vegetable foods. They have a molecular weight of 14 kDa and present a high degree of structural homology as well as marked cross-reactivity among one another. The presence of anti-profilin IgE broadens the spectrum of sensitizations to vegetable foods detected through

skin tests and/or in vitro tests but it is unclear whether it is connected with the clinical expression of food allergy (Fernández Rivas, 2003).

Food intolerance

Patients suffering from AD who are sensitized to a food protein can show not only the reactions of food allergy, but reactions described as food intolerance. As mentioned above, *food intolerance* is a reaction to food, where the immune system is not included, even though the symptoms are similar to those of IgE-mediated allergic reactions. Both kinds of these reactions to foods (food allergy reactions and food intolerance) are summarized under the term of food hypersensitivity reactions. In food intolerance, an impaired histamine degradation based on reduced diaminoxidase activity and the resulting histamine excess may cause numerous symptoms mimicking allergic reactions. The ingestion of histamine-rich food or of alcohol or drugs that release histamine or block diaminoxidase activity may provoke diarrhea, headache, rhinoconjunctival symptoms, asthma, hypotension, arrhythmia, urticaria, pruritus, flushing, and other conditions in patients with histamine intolerance. Dermatologic sequels can be rashes, itching, urticaria, angioedema, and AD. In addition to histamine-rich food, many foods such as citrus foods, are considered to have the capacity to release histamine directly from tissue mast cells, even if they themselves contain only small amounts of histamine (Maintz & Novak, 2007; Maintz et al., 2006). Some studies described food hypersensitivity reactions without differentiating between food allergy and food intolerance.

According to Mattila food hypersensitivity is commonly suspected, especially among adults with atopic diseases (Mattila et al., 2003). In the study of Mattila, 286 Finnish university students were examined; 87 of them without clinically confirmed atopic disease, the rest suffered from AD/or other atopic diseases (Mattila et al., 2003). A thorough clinical examination was performed with a questionnaire specifying adverse events to foods, food hypersensitivity was recorded in 172 subjects (60%), most frequently among subjects with AD and other atopic diseases (Mattila et al., 2003). The authors stressed that more data are needed regarding patient groups at risk for food hypersensitivity and symptoms and foods responsible for the reactions (Mattila et al., 2003). The Roehr's study presents the data of the pediatric group (0–17 years) of a representative, randomly sampled, cross-sectional population – a survey studying 13,300 inhabitants of Berlin regarding food-related symptoms (Roehr et al., 2004). They concluded that the perception of food-related symptoms is common among children and adolescents from the general population. Self-report could be confirmed in around one of 10 individuals, still resulting in 4.2% of proven clinical symptoms. However, most reactions were mild and mainly because of pollen-associated food allergy while non-allergic food hypersensitivity reactions were less common. Severe IgE-mediated food allergy was observed in individuals with preexisting atopic disease (Roehr et al., 2004). According to the results of Osterballe, rising prevalence of food hypersensitivity and severe allergic reactions to foods have been reported; this study estimated the prevalence of food hypersensitivity to the most common allergenic foods in an unselected population of young adults (Osterballe, Mortz, Hansen, Andersen, & Bindslev-Jensen, 2009). They investigated a cohort of 1272 young adults, 22 years of age, by a questionnaire, skin prick test, and histamin release followed by oral challenge to the most common allergenic foods. Food hypersensitivity was divided into primary and secondary, primary food hypersensitivity was defined as being independent of pollen sensitization whereas the

secondary one was defined as a reaction to pollen related fruits and vegetables in pollen allergic patients. The primary food hypersensitivity was reported by 19.6% and the secondary one by 16.7% of the participants. Confirmed primary food hypersensitivity by oral challenge was 1.7%. In primary food hypersensitivity, the most common allergenic food was peanuts (0.6%) followed by additives (0.5%), shrimps (0.2%), codfish (0.1%), cow's milk (0.1%), octopus (0.1%), and soy (0.1%). In secondary food hypersensitivity, kiwi allergy was reported by 7.8% of the participants followed by hazelnut (6.6%), pineapple (4.4%), apple (4.3%), orange (4.2%), tomato (3.8%), peach (3.0%), and nuts (2.7%), (Osterballe et al., 2009). The aim of other Osterballe study was to estimate the prevalence of food hypersensitivity to the most common allergenic foods in an unselected population of children and adults (Osterballe, Hansen, Mortz, Host, & Bindselev-Jensen C, 2005). In total, 698 cases of possible food hypersensitivity were recorded in 304 (16.6%) participants. The prevalence of food hypersensitivity confirmed by oral challenge was 2.3% in children at 3 years of age, 1% in children older than 3 years and 3.2% in adults. The most common allergenic foods were hen's egg affecting 1.6% of 3-years-old children and peanuts in 0.4% of adults. Of the adults, 0.2% was allergic to codfish and 0.3% to shrimp whereas no challenges with codfish and shrimp were positive in children. The prevalence of clinical reactions to pollen-related foods in pollen-sensitized adults was estimated to be 32% (Osterballe et al., 2005). According to the Kanny's study, food allergy is an important health problem for which epidemiologic studies are needed. They performed an epidemiologic survey in France to determine the prevalence, clinical pictures, allergens, and risk factors of food allergy. This study was conducted on 33,110 persons who answered a questionnaire addressed to a representative sample of the French population. The reported prevalence of food allergy is 3.5% and 57% reported atopic diseases. The most frequent allergens were 14% rosaceae, 9% vegetables, 8% milk, 8% crustaceans, 5% fruit cross-reacting with latex, 4% egg, 3% tree nuts, and 1% peanut. Sensitization to pollen was significantly related to angioedema, asthma, rhinitis, and fruit allergy. The main manifestations of food allergy were AD in subjects under 6 years of age, asthma in subjects between 4 and 6 years of age, and anaphylactic shock in adults over 30 years of age (Kanny et al., 2001). According to Roehre, it is well known, that objective clinical symptoms can be reproduced in only a small proportion of subjective reports, probably because of a strong tendency of individuals to casually relate situations of the daily life with ingested foods (Roehr et al., 2004). Symptoms, such as pruritus and worsening of AD, do not always have a connection with ingested foods but patients may relate them to foods. Retrospective analyses by Breuer have shown that the patient's history of food related AD does not have a high diagnostic importance (Breuer et al., 2004).

Atopic march

Many epidemiological investigations have suggested that food allergy is a risk factor for the appearance of other allergic disease in later childhood (Kijima et al., 2013; Penard-Morand et al., 2005; Ricci et al., 2010) and the progression of atopic disorders from AD in infants to allergic rhinitis and asthma in children is usually described as atopic march (Burgess et al., 2007; Carlsten et al., 2013; Leynaert et al., 2004; Ricci et al., 2006). The most important factor that precipitates allergic march is now considered an impaired epidermal barrier. Barrier disturbances result from genetic defects (Palmer et al., 2006; Weidinger et al., 2006) and early epicutaneous sensitization to food and aeroallergens

may be enhanced by damage of the skin barrier function (Schäfer, 2008; van den Oord & Sheikh, 2009). There is a clear evidence of a relationship between filaggrin gene (FLG) mutations and AD; FLG also increases the risk of asthma bronchiale with AD and the risk of allergic rhinitis with/without AD (van den Oord & Sheikh, 2009). Abnormal expression of epidermal proteins caused by Th2-type cytokines or protease allergens may increase the risk of sensitization to allergens and contribute to the development of AD (Howell et al., 2007; Kim et al., 2008; Wan et al., 1999, 2001).

For many years, traditional recommendations for food allergy prevention included avoidance of allergenic foods during the first several years of life. However, evidence suggesting a more crucial role for allergen sensitization through an impaired skin barrier together with studies suggesting a possible protective role for early allergen oral tolerance had called these recommendations into question (Shaker, 2014). For example, peanut allergy has been found to be more likely if children are treated with skin preparations containing peanut oil (Lack, Fox, Northstone, & Golding, 2003).

According to some studies, food allergy that developed at a young age increased the risk of AD, asthma bronchiale, and allergic rhinitis at 8 years of age (Östblom, Lilja, Pershagen, van Hage, & Wickman, 2008), in 9 to 11-year-old children food allergy was highly associated with asthma bronchiale and allergic rhinitis (Penard-Morand et al., 2005).

There is a lack of reports focusing on long-term studies of the clinical and allergometric evaluations observed during the course of AD with respect to its evolution and association with allergic responses in affected patients.

According to our results, adolescent and adult patients suffering from food hypersensitivity reactions in general suffer significantly more often from rhinitis and from persistent eczematic lesions; the dependence was confirmed in patients with hypersensitivity reactions to nuts, kiwi, fishes and apple (Čelakovská & Bukac, 2015). Regarding the role of food allergy in atopic march, AD patients with confirmed food allergy suffer significantly more often from rhinitis, asthma bronchiale, persistent eczematic lesions, pollen allergy and have positive data about atopy in their family history. Peanuts, soy, and wheat are of great importance (Čelakovská, Bukac, & Ettler, 2015).

The early childhood is thought to be a key period for the prevention of allergic march, adolescence is another key period for the prevention of recurrence. The prevention of recurrence would decrease allergic disease in adulthood. Further prospective studies using large cohorts are necessary to assess this issue (Kijima et al., 2013). Furthermore, Ricci et al. reported that the integrated management of AD decreases the likelihood that affected children would progress toward respiratory allergic disease (Ricci et al., 2010). Thus, prompt management of AD and food allergy that develop in early infancy may be a successful method for preventing allergic march.

Prevention of AD

According to summary of key findings from 24 systematic reviews of AD about the primary prevention of AD, epidemiological evidence points to the protective effects of early daycare, endotoxin exposure, consumption of unpasteurized milk, and early exposure to dogs, but antibiotic use in early life may increase the risk for AD. With regard to prevention of AD, there is currently no strong evidence of benefit for exclusive breastfeeding, hydrolysed protein formulas, soy formulas, maternal antigen avoidance,

omega-3 or omega-6 fatty-acid supplementation, or use of prebiotics or probiotics (Torley, Futamura, Williams, & Thomas, 2013).

Conclusion

The early onset of AD was found to be associated with high-risk IgE levels in food allergy. The most important factor that precipitates AD and allergic march is an impaired epidermal barrier. The increased skin permeability may increase the risk of sensitization to food and other allergens, this pointing to the possible role of cutaneous allergen avoidance in early life to prevent the onset of AD. Early childhood is thought to be a key period for the prevention of allergic march, adolescence is another key period for the prevention of recurrence. The prevention of recurrence would decrease allergic disease in adulthood.

Disclosure statement

No potential conflict of interest was reported by the author.

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