

Allergens in Atopic Dermatitis

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Abstract Allergens play an essential role in atopic dermatitis, either intrinsic or extrinsic. They provoke cutaneous inflammation via IgE-dependent and cell-mediated immune reactions. Food allergens have a well-known contribution to disease activity of atopic dermatitis, especially in infants and young children. However, the importance of inhaled allergens is still under investigation. For clinical implication, identification of individualized allergens is an ideal strategy for better control of atopic dermatitis and avoidance of atopic march. The aim of this article is to discuss the common allergens in atopic dermatitis (AD), the specificity and sensitivity of laboratory tests for allergens, and the clinical effect of various preventions.

Keywords Allergy · Allergens · Atopic dermatitis

Overview

Atopic dermatitis (AD) is not simply a constitutive skin defect. Its major pathogenic factors are immunologic abnormalities, especially from interactions with various allergens. By clinical observations, allergens have given lots of reports about its correlation with the signs and symptoms of AD. Moreover, AD skin has a marked impairment in barrier function mainly caused by decreased ceramide levels and resulting in enhanced transepidermal water loss [1]. The epidermal changes contribute to increased antigen absorption into the skin. Compared to systemic or airway allergic disorders, transcutaneous sensitization to allergen results in higher level of TH2 responses [2, 3].

It has been well-known that food, inhaled and contact allergens contribute to exacerbation of eczema in AD patients. Cow's milk and hen's eggs can provoke flare in infants and young children with AD, whereas inhaled allergens, pollen-related foods, and contact allergens are of greater importance in older children, adolescents, and adults [4].

However, AD is classified as intrinsic and extrinsic. Intrinsic AD does not have a high level of IgE (<300 kU/l), and express several humoral and cellular profiles different from those of extrinsic AD. Extrinsic AD usually has high IgE level, allergen-specific IgE, and significant clinical response to environmental allergens. Although positive atopy patch test (APT) is believed to be an allergen-specific IgE-mediated reaction via the Langerhans' cells in the epidermis, intrinsic AD patient could also have positive APT reactions. It may be evoked by proteases in the mite extract [5]. In 2004, Holm showed that intrinsic AD patients with positive APT to mite extract had increased number of IgE+ cells and FcεRI+ cell in the epidermis. Therefore, the role of allergens in intrinsic AD still needs to be clarified by long-term investigation [6].

IgE-Dependent Activation of T Cells by Allergens in AD

Both IgE-mediated immediate immune response and T-cell-mediated delayed immune response are involved in AD skin reactions to allergens. AD skin contains an increased number of IgE-bearing Langerhans cells (LC) that appear to play an important role in cutaneous allergen presentation to TH2 cells [7]. The cell-bound IgE on LC facilitates capture and internalization of allergens into LC prior to their processing and antigen presentation to T cells. IgE-bearing LC that have captured allergen likely activate memory TH2 cells in atopic skin, but they may also migrate to the lymph nodes to stimulate naïve T cells to further expand the pool of systemic TH2 cells. Normal individuals and patients with respiratory allergy have low-level surface expression of

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Fc ϵ RI on their LC, whereas Fc ϵ RI is expressed at high levels in the inflammatory environment of AD. In 2004, Cooper [8] demonstrated the interaction between allergen and IgE in allergen-mediated activation of T lymphocyte from patients with AD. He showed that the response to allergen of unmodified peripheral blood mononuclear cells (PBMC) from individual AD patients are significantly greater in the presence of fresh, unheated, IgE-containing autologous serum than the same serum heated under IgE-denaturing conditions or specifically depleted of IgE by immunoprecipitation. It provided the first evidence that sufficient amounts of allergen-specific IgE and allergen-reactive T cells occur concomitantly in the blood of individual AD patients to allow IgE-enhanced T-cell responses to allergen.

Food Allergen

The natural history of sensitization in allergies reflects the well-known allergy march starting in early infancy with atopic dermatitis often related to food allergy during the first 1–3 years of life followed by partial recovery of these allergic diseases, which are replaced by bronchial asthma and allergic rhino-conjunctivitis in later childhood and adolescence [9]. The relatively high incidence of food allergy, especially cow's milk allergy, in infancy has been suggested to be the result of a defective mucosal barrier, increased gut permeability to large molecules, and immaturity of local and systemic immunological response [9].

Several studies have shown the immunopathophysiology of food allergy. Man [10] reported that systemic and gastrointestinal-derived dendritic cells (DCs) from allergic mice had an increased resistance to T-cell-mediated apoptosis compared with that seen in control mice. They also found the T-cell-mediated DC apoptosis is antigen-specific and MHC class II dependent. Thus, these evidences supported a role for an antigen-specific malfunction in regulatory pathway.

Prevalence of Food Allergy in AD

In western countries, the prevalence of food allergy is estimated to be 2–3% in adults and 6–8% in children. The prevalence rate is much higher in patients with AD. Eigenmann reported an unselected survey performed at a university dermatologic clinic reported that 37% of unselected children with mild to moderate AD had food allergy [11]. The overall prevalence of food allergy in infants with AD ranged from 20 to 80% in various studies, and may be estimated at 30%. Guillet found that severe AD and younger age are risk factors for food allergy [12]. Clinical symptoms of patients with food-sensitive AD often improve with an increase in age [13]. Woods reported that

prevalence of food allergy in 41 randomly selected young adults is 1.3% [14]. Allergy to some foods (such as egg and cow's milk) is relatively transient, whereas allergy to peanuts or shellfish may persist through life [15]. Ingestion of foods at an early time point in atopic infant may enhance the risk for sensitization to these foods. Sensitization to peanut protein may also occur in children via emollient-containing peanut oil [16].

There is still controversy about food allergy in AD, because most of the surveys were evaluated by allergist/immunologist, not including dermatologist. However, some studies demonstrated ingested food antigens could penetrate the digestive tract barrier and were transported in the blood stream to mast cells in the skin [17, 18]. The first murine model of an AD-like disorder induced by oral sensitization with a food protein has been established in 2001 [19].

The prognosis of food allergy is well, with the majority of children becoming tolerant over time. Thus, children should be reevaluated at regular time intervals. For cow's milk and hen's egg allergy, 12–18 months may be practical. However, for peanut and tree nut allergies that are not often outgrown, longer time intervals may be meaningful [20]. Approximately 20% of young children will experience resolution of their peanut allergy by school age [21]. Fleischer [22] followed patients with resolved peanut allergy and found 8% had recurrence.

Common Food Allergens

Hen's egg, cow's milk, wheat, soy, shellfish, fish, and peanut are the most common offending foods. The first four allergens account for about 90% of allergenic foods in children with AD.

Soy protein is reported to be at least as allergenic as cow's milk protein, and in young children with cow's milk protein allergy, soy protein allergy has been estimated with frequencies between 17 and 47% [23, 24]. Therefore, soy formula is not recommended for infants and young children with cow's milk protein allergy. Moreover, most of the proteins of goat's milk share identity with those of cow's milk, resulting in cross-reactivity [25].

Patterns of Clinical Reactions to Foods in AD

Food allergens may induce eczematous dermatitis or urticarial lesions in the skin. Sometimes extracutaneous symptoms and signs also appeared. IgE-mediated food allergy in AD patients presented as urticaria and angioedema are easily to be recognized, but they may be less than 10% of all food allergies in AD. The delayed-type reactions of food allergy cause exacerbation of AD, which are eczematous lesions, usually occurring after 6–48 h [15, 26].

Tests for Food Allergens and Their Predictive Values

The diagnostic work-up of suspected food allergy starts with a detailed patient history and physical examination of the patient. The further work-up of the patient includes various *in vitro* and *in vivo* tests, usually measurement of food-specific IgE antibodies, skin prick test (SPT), atopic patch test (APT), elimination diet, and oral challenge test [20].

In IgE test, crude allergen extracts used in IgE tests are not optimal for allergy diagnosis, and the diagnostic criteria for several food, for example, wheat and soy could not be established. Especially, the age of patients appears to play an important role [27, 28].

Immediate-type allergy skin testing (SPT) is based on allergens binding to specific IgE antibodies, which are attached to mast cells, leading to release of intracellular mediators, including histamine. The mediators result in the immediate formation of a wheal and flare (swelling and erythema), resembling the natural response to a mosquito bite. The wheal depends upon histamine binding to histamine receptors on the microvasculature, resulting in increased vessel permeability, while the flare is the result of neurogenic vasodilatation. This response is required more for sensitization than for clinical allergy. Compared with a negative control (diluent only) and a positive control, usually a standard dose of histamine, applied in a similar manner. Levels of significance, relating to the extent of allergen sensitivity, have been ascribed to the diameter of the wheal and/or the flare and the ratio of the response to histamine control [29]. Allergy skin test response therefore reflects the presence of allergen antibodies bound to mast cells.

A positive skin test to an allergen does not demonstrate that the allergen is the cause of a particular clinical illness. A parable might be a positive response to a test for elephant allergy in a person who is not exposed to elephants. This positive test is not clinically relevant.

A positive test may also indicate sensitization to an allergen at a level too low to cause symptoms, an exposure to an allergen in the past, or an allergen that is an irritant or contains impurities that are irritants. Sensitization describes the existence of specific antibodies to a substance, as exemplified by a positive response to a skin test. This response reflects sensitization, but not clinical allergy.

Food allergen skin testing results in false positive allergy tests more frequently than aeroallergen skin testing. Before concluding that a positive allergy skin test is clinically relevant, there must be either conclusive historical evidence that exposure to the allergens caused the symptoms present or a provocation test confirming the clinical sensitivity. There are numerous examples of individuals having positive skin test to foods, yet they can ingest the food with impunity. Allergy skin testing may also be negative when there is clear adverse response to a suspected

allergen. Irritant responses to airborne particles or volatile organic compounds and food intolerance are examples [30].

The diagnostic criteria of skin prick test (wheal diameters) have been described for milk, egg, fish, peanut, but not wheat, soy. Moreover, the diagnostic decisions varied widely between study populations.

Recently, there are evidences showing the use of purified or recombinant allergens, instead of whole food allergen extracts, may give more accurate results in allergy tests. For example, IgE to wheat allergen ω -5 gliadin was shown to be correlated well with oral challenge test [31]. IgE to Ber e1 was correlated with clinical expression of allergy to Brazil nut [32]. The use of purified or recombinant allergens, instead of whole food allergen extracts, might give more accurate results in a food allergy diagnosis. Besides, comparisons between microarray-based immunoassays and the Pharmacia CAP system showed a good correlation for food and aeroallergens [33, 34]. Microarray assays have at least three important advantages over the traditional methods used in IgE tests. First, they could screen hundreds of allergens at the same time; second, they require a minute amount of serum; third, microarray assays need much less allergen [35].

Placebo-controlled food challenges (DBPCFCs) are the gold standard for allergy test, because there are many limitations for *in vitro* tests. The major disadvantages of DBPCFC are risk of anaphylaxis and time consuming, costly, and stressful procedures [35].

Serum-specific Immunoglobulin E (IgE) Level

Whether the amount of total IgE should be taken into account in the interpretation of food-specific IgE levels has been recently evaluated. It was shown that the determination of the ratio of specific IgE: total IgE for diagnosing symptomatic food allergy offers no advantage for cow's milk, hen's egg, wheat, or soy [36]. False positive results are frequently seen in screening for anti-food IgE antibodies, especially in patients sensitized to pollens or latex.

The IgE-binding epitopes for all casein and whey allergens in cow's milk have been found [37–40]. Ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovomucoid (Gal d 3), and lysozyme (Gal d 4) have been identified as major hen's egg allergens [41]. Ovomucoid is the major allergen in hen's egg, and children with persistent egg allergy have a higher level of IgE anti-ovomucoid antibodies than those who "outgrow" their reactivity [42]. In contrast to the other three major allergen in hen's egg, ovomucoid is relatively resistant to heat and digestive enzyme [43].

For peanut allergy, the major and minor allergens have been identified. They are peanut conglutins Ara h 2, 6, and

7, the peanut vicilin Ara h1, the peanut glycinin Ara h 3/4, and the peanut profiling Ara h 5 [44–47].

The major soybean allergens are seed storage proteins including glycinin G1 and G2, β -conglycinin, and soy profiling Gly m 3 [41]. It has been reported that the soybean blycinin G1 acidic chain shares IgE-binding epitopes with the peanut allergen Ara h 3 [48].

The muscle protein tropomyosin has been identified as the major allergen in shellfishes, such as shrimp, crab, crawfish, and lobster [49]. Allergenic tropomyosin I is found not only in shellfishes, but also in house dust mites and cockroach, suggesting tropomyosin as an important cross-sensitizing pan allergen [47]. Moreover, based on amino acid similarities and epitope reactivity, lobster tropomyosin has the greatest and cockroach tropomyosin the least cross-reactivity with shrimp [50].

The majority of children with immediate allergic reactions to ingested wheat had IgE antibodies to ω -5 gliadin [31], which is identified as a major allergen in wheat-dependent, exercise-induced anaphylaxis [51].

Infants and young children with moderate to severe AD generally have positive immediate skin tests or serum IgE directed to various foods (even in cases with normal total serum IgE levels). Celik-Bilgili [27] performed a controlled 992 oral challenge tests (728 challenges were double-blind, 264 challenges were open) and measurement of serum specific IgE level in 501 children (88% of them fulfilled the diagnostic criteria for AD, aged from 1 month to 16.1 years) to determine the predictive value of specific serum IgE for outcome of oral challenge. They found that sensitivity for specific serum IgE was 97% for hen egg, 83% for cow's milk, 79% for wheat, and 68% for soy. Specificity was 51% for hen egg, 53% for cow's milk, 50% for soy, and 38% for wheat. Pourpak [52] reported cow's milk allergy increased the severity of AD, eosinophil count, and total serum IgE level.

A major research goal is the prediction of clinical reactivity, the nature course, and severity of a food allergy by food-specific IgE test. In regard to the severity of a food allergy, laboratory parameters have been a poor predictor [21]. Shek reported a study of food challenge and food-specific IgE levels of milk and egg in young children over time [53], which showed the rate of decrease was predictive for the development of tolerance in children aged below 4 years at first challenge. They also establish mathematical models that could predict the timing of resolution of food-specific allergy.

Skin Prick Test (SPT)

SPT is a method of immediate-type allergy testing. Careful examination of the skin prior to skin testing is important, and a sun-protected healthy skin area is preferred [30]. With foods, the use of native allergens

seems to be superior to commercial extracts [54]. Comparing results from different studies, the SPT techniques and the source of allergens used should be considered. As in food-specific IgE test, a lot of effort has been made to develop diagnostic decision points. Similar to the measurement of food-specific IgE, no decision points could be determined for soy, and only in a subset of patients for wheat [36].

Hill reported 555 open food challenges in 467 children showed a food-specific SPT wheal diameter of at least 8 mm for cow's milk, 7 mm for hen's egg and 8 mm for peanut was 100% diagnostic for allergic reactions using certain commercial extracts [55]. Besides, in children of less than 2 years of age, the corresponding wheal diameters were 6.5 and 4 mm, respectively [55]. Using native allergens, a 735-oral-food challenge performed in a German population showed positive predictive decision points of 13 mm were determined for hen's egg and cow's milk, respectively [56].

Atopic Patch Test (APT)

APT is an informative and reliable diagnostic test in evaluating delayed type allergic reactions. When there is neither elevated level of IgE nor positive skin prick test, food allergy should be further investigated by making a patch test [57]. Moreover, for wheat allergy, for which measurement of specific IgE and SPT gives unsatisfactory results, the APT proved to be the most reliable test, and the positive predictive value of 94% could not be improved by a combination with other allergy tests [58]. In 1996, Isolauri first reported that a combined skin prick and patch test enhances the diagnosis of food allergy in AD infants [59]. Rokaite found that positive skin patch test is most often found in children from 6 months to 7 years of age [57]. Darso reported a European multicenter study showed that the APT had a higher specificity than SPT or specific serum IgE [60]. However, Hansen *et al.* [61], Breuer *et al.* [62] and Osterballe *et al.* [63] showed that APT could not predict food hypersensitivity not predicted by SPT or specific IgE measurement. These controversial data might be explained by the fact that the APT is sometimes difficult to interpret, with non-specific reactions occurring frequently. Therefore, the European Task Force on Atopic Dermatitis (ETFAD) has developed a standardized APT technique. It consists of purified allergen preparations in petrolatum, applied in 12-mm diameter Finn chambers mounted on Scanpor tape to non-irritated, non-abraded, or tape-stripped skin of the upper back. The APT is read at 48 and 72 h according to the test criteria and reading key of the ETFAD for appearance of erythema, and number and distribution pattern of the papules. In contrast with skin prick test, the APT might detect a relevant sensitization in the absence of

specific IgE. Therefore, a lot of studies have been undertaken to determine the sensitivity and specificity of the APT [64].

Oral Challenge Test (OCT)

Positive skin tests to allergens do not always indicate clinical sensitivity in AD patients. Therefore, clinically relevant food allergy must be verified by controlled food challenges or carefully investigating the effects of a food elimination diet that is being done in the absence of other exacerbating factors.

Oral challenge test (OCT) is the gold standard for diagnosing food allergy, which should be always done under medical supervision. Double-blind, placebo-controlled food challenge (DBPCFC) represents the best procedures of OCT, which include: (1) a wash-out period for suspected allergenic food—provided food are avoided on the basis of skin test or a highly suggestive history of food allergy. These suspected foods are removed from diet for 7–10 days before admission; (2) withdrawal of interfering medications: oral corticosteroids for least 1 month, antihistamines for at least 7–10 days, beta-adrenergic drugs for 8 h; (3) the pre-existing skin lesions are treated with aggressive skin care for 3 days before oral challenges, which include two to three soaking baths or wet raps per day, followed by the application of an emollient to the whole body and topical corticosteroids. Antibiotics can be applied if staphylococcal infection is suspected. Chloral hydrate is used for sedation, and a venous line was set for providing an access for management of complications (such as anaphylaxis); (4) allergens should be given as a double-blind, placebo-controlled food challenge (DBPCFC) [65] in a randomized order using a titrated approach with two allergens and one placebo. The observation period should be 48 h; (5) to confirm negative food challenges, all patients were fed the food openly in a meal form under observation prior to discharge. Most of the symptoms occurred between 5 min and 3 h after food challenge, and late-phase reactions are between 6 and 28 h.

Only about one third of positive skin tests correlated with positive food challenges.

Other Laboratory Studies

Food allergen-specific T cells have been cloned from the skin lesions of patients with AD [66]. Children with AD who are chronically ingesting allergic foods have increased spontaneous basophil histamine release compared with children without food allergy [2]. Positive food challenges result in increased plasma histamine levels, and eosinophil activation were also seen at OCT.

Casein-reactive T cells from patients with cow's-milk-induced eczema were found to have significantly higher levels of CLA than *Candida albicans*-reactive T cells from the same patients, casein- or *C. albicans*-reactive T cells from nonatopic controls, or noneczematous controls with milk-induced gastroenteropathy.

Overall, these studies provide strong scientific evidence that foods can play a role in the pathogenesis of AD in young children. Most food allergic children, however, outgrow their food hypersensitivity in the first few years of life, so food allergy is not a common trigger factor in older patients with AD.

Implications for Clinical Practice

If food allergy is suspected, the child should be referred to a pediatric dietitian [14]. There have been several solutions for children with food allergy and severe AD.

Breast Feeding

Typically, breast-feeding (BF) can decrease the severity of atopic eczema, but not prevent its occurrence. It is widely recommended for the first 4–6 months. Human colostrum/milk facilitates maturation of the gut and provides passive protection against infectious agents and antigens [23]. Moreover, proteins absorbed from the gut can be measured in the blood in children and adults. Food proteins are also found in the breast milk. For the purpose of avoidance of cow's milk protein and common food allergens, the joint statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) is that “exclusive breast-feeding during the first four to six months of life might greatly reduce the incidence of allergic diseases” [23]. However, most of the long-term studies focus on the symptoms of children beyond infancy. Thus, respiratory atopy is the main variable in these analyses. Moreover, randomized controlled study of breast-feeding in early neonatal period is not common and questionable in ethics [67].

However, some infants do not benefit from BF, and may be even worsened by BF. A study from a German Multicenter allergy (MAS) showed that the presence of AD in the first 7 years of life increased with each additional month of breast-feeding [68]. Wetzig also reported the association between the duration of breast-feeding and the development of atopic diseases [69]. He also found a significant association between the duration of breast-feeding, sensitization to egg, and atopy. Children who had been exclusively breast-fed for at least 5 months were more frequently sensitized to egg, and AD was more frequently diagnosed. Therefore, the clinician should keep in mind that

withdrawal of BF from a refractory eczematous infant may be of great help because most of these infants are already sensitized to common foods [70].

Hypoallergenic Formulas

Hypoallergenic formulas are processed by enzymatic hydrolysis of different proteins in cow's milk. So far there are no firm criteria available for the design of hypoallergenic foods for prevention. A lot of randomized controlled studies have been done over the last two decades to investigate the preventive effect of hydrolyzed formula. For example, Chandra [70, 71] compared the development of asthma, AD, and food allergy in groups of children fed breast milk, hydrolyzed formula, cow's milk formula, and soy formula. A marked preventive effect of breast milk and partially hydrolyzed formula was noted consistently up to the age of 5 years.

Studies have shown that extensively hydrolyzed milk has a greater preventive effect than partially hydrolyzed milk. Thus, there is some controversy regarding the extent of hydrolysis needed for primary prevention [72]. For secondary prevention, in children with cow's milk allergy, it is agreed that only extensive hydrolysate should be used [72].

If breast-feeding for 4–6 months is not possible in high-risk babies, a documented hypoallergic formula and avoidance of solid foods are recommended for the first 4 months of life [73]. Finally, no known data indicated that hydrolyzed formula is superior to breast milk in the prevention of AD [74].

Elimination Diet

Maternal Avoidance Diet During Pregnancy

A lot of studies have investigated the preventive effect of elimination diet during pregnancy. They often showed that avoidance of highly allergenic foods, such as cow's milk, hen's egg, fish, soy, and nuts, during pregnancy does not have long-term protective effect against the development of atopic diseases in high-risk children [75, 76]. A Cochrane database review concluded that restricting maternal diet during pregnancy does not prevent allergy and might have adverse results for maternal nutrition, fetal nutrition, or both [77].

Maternal Avoidance Diet During Lactation

Maternal food allergen avoidance during lactation might be of some benefit [78–81]; however, Hermann [82] failed to show a protective effect of maternal avoidance diet (cow's milk and hen's egg) during pregnancy and lactation. None of the studies reported any adverse nutritional effects for mother or child.

Late Introduction of Solid Food

In a 10-year longitudinal study, Fergusson showed that introduction of solid foods before this age of 4 months might increase the risk of AD in genetically predisposed children [83]. However, there are several reports against the beneficial effect of late introduction of solid food [84, 85].

Avoidance of Allergenic Foods in Older Children

For older children, removal of food allergens from the patient's diet can lead to significant clinical improvement, but requires a great deal of education because most of the common allergens (e.g., egg, milk, wheat, soy, and peanut) contaminate many foods and are therefore difficult to avoid [86]. Artherton observed a significant improvement in more than 50% of children during dietary exclusion [87]. Several other studies also show good response to food elimination. However, there are major problems in these studies: study design (open-labeled vs. double-blinded), patients' age, and methods (evaluations upon immediate reaction vs. late reaction, and diagnostic tests). In addition, the cellular response to crude peanut was also down-regulated in the soy immunotherapy group [88].

Strategies to Induce a TH-1 Cytokine Profile

Pohjavuori [89] reported that infants with suspected cow's milk allergy had significantly lower secretion of IFN- γ by peripheral blood mononuclear cells (PBMC) than infants without cow's milk allergy. After feeding with *Lactobacillus* GG, increased level of secreted IFN- γ in the infant with cow's milk allergy was noted. In an atopic dog with food allergy, Frick [90] demonstrated that immunotherapy with a combination of TH-1 promoting bacteria (heat-killed *Listeria monocytogenes*) and food allergens could reduce or eliminate the symptoms of food challenge and levels of food-specific IgE.

Others

One strategy attempted for peanut allergy was to use soy, a legume with homologous proteins to peanut, but may not have the potential to trigger allergic reactions, as immunotherapy in a murine model.

Inhalant Allergen

The Importance of Aeroallergens in AD

In 1949, Tuft found that most adult patients with AD had positive skin tests to "autologous" house dust. He also

noted that inhaled dust could cause exacerbation of skin symptoms, which was then improved by cleaning the house [91]. Walker noted that several of his patients had exacerbation of AD following exposure to horse dander, timothy grass, or ragweed pollen [92]. Tuft and co-workers reported that in patients with AD, pruritus and eczematoid skin lesions developed after intranasal inhalation challenge with either *Alternaria* or ragweed pollen, but not placebo [93]. Tupker reported double-blind, placebo-controlled challenges have demonstrated that inhalation of house dust mites by bronchial challenge can result in new AD skin lesions and exacerbation of a previous skin rash [94]. Schafer reported that the degree of sensitization to aeroallergens is directly associated with the severity of AD [95].

Although evidence showed that aeroallergens played a role in AD, there are some clinical observations against the importance of aeroallergens in AD. For example, aeroallergens could not evoke eczematous lesions in skin testing is quite common. Immunotherapy with suspected aeroallergens was not effective for AD.

There is conflicting data regarding whether dust mite allergens have their primary role through direct contact with the skin or whether inhalation and absorption through the respiratory tract is equally important [96]. It has been known that patients with AD have increased sensitivity to irritant. Further, house dust mite allergen is a cysteine proteinase, which may function not only as an allergen [97]. However, Carswell found that serum concentration of mite-specific IgE were greater in children with AD than children with bronchial asthma. They concluded that increased exposure to mite allergens was a result of skin inflammation and thus the high level of mite-specific IgE provided an evidence for cutaneous sensitization [98]. On the other hand, Tupker demonstrated a double-blind, randomized, placebo-controlled trial, which showed inhalation of house dust mite could induce new skin lesions and exacerbation of existing lesions in AD [94].

Common Aeroallergens

Mites, fungus, animal dander, pollens, cockroach are common aeroallergens.

In fact, it has been difficult to have controlled studies for aeroallergens other than dust mite. Patch test results have supported a role for other aeroallergens, but not as frequently as dust mite.

Tests for Inhalant Allergens and Their Clinical Correlation

Serum-specific IgE Level

In most patients with AD, IgE antibody to specific inhalant allergens has been noted for years. The greatest concentration

of IgE in AD patients is specific for dust mite. A recent study found that 95% of sera from AD patients had IgE to house dust mites as compared to 42% of asthmatic subjects. Moreover, the concentrations of IgE to dust mite allergens in patients with AD were usually at least 20-fold higher than those of patients with asthma [99]. Even in patients with “pure” AD, very high levels of IgE were not uncommon. However, there is still controversy about the association of severity and IgE level in AD patients. Some experts still consider that elevated IgE in AD patients may be simply an incidental finding or a result of abnormal B-cell regulation [100].

Atopy Patch Test (APT)

Epicutaneous application of aeroallergens by patch test techniques on uninvolved atopic skin elicits eczematoid reactions in 30 to 50% of patients with AD [99]. Positive reactions have been observed to various aeroallergens, including dust mite, weeds, animal danders, and molds. In contrast, patients with respiratory allergy and healthy volunteers rarely have positive allergen patch tests.

Although exacerbation of skin lesions in AD patients has been elicited by allergen challenge via airway or skin. However, none of them could provide a consistent model in which the response of the skin to allergens could be studied [100]. Perhaps the best method reported so far for studying the role of inhalant allergens in AD has been the patch test [100]. However, in a study of 52 AD patients, Heinemann [101] found that the reproducibility rate of APT was 56.3%. Bygum [102] also demonstrate a similar result in a study of 23 AD patients and 25 healthy controls.

Mitchell stripped the skin before APT, which resulted in a consistent eczematous reaction in AD patients at 48 h. This pattern of reaction was limited to AD patients who had a positive immediate skin reaction to the same allergen [5].

From AD skin lesions and allergen patch test sites, Wheatley isolated T cells that selectively respond to *Dermatophagoides pteronyssinus* and other aeroallergens provide. Therefore, immune response in AD skin can be elicited by aeroallergens [103]. However, the major problems of APT are its variable reproducibility reported from different study groups and methods [104].

In intrinsic AD, aeroallergens cannot be determined by standard skin prick tests or serum IgE determination. In 2003, Ferschenlohr [105] used APT to investigate the clinically suspected role of aeroallergens in three patients with intrinsic AD. Two patients developed strongly positive (+++) APT reactions for the house dust mite allergen, while the other patient had a markedly positive (++) APT reaction to birch pollen. A serum IgG response—mainly IgG4—to house dust mite allergen was detected in the patients with positive APT to mite. Their sera demonstrated major sIgG4 reactivity to a 28-kd allergen (corresponding to Der p 3).

The other patient with positive APT reaction to birch pollen had neither sIgE nor sIgG4 reactivity to birch pollen and house dust mite allergens. Thus, they concluded that aeroallergens might be a relevant pathogen for intrinsic AD, even in the absence of detectable aeroallergen-specific serum IgE and negative skin prick test results. And, APT might become an important diagnostic tool, especially in patients with intrinsic AD in who skin prick test and serum IgE tests do not identify allergens relevant to the clinical course of disease.

Implications for Clinical Practice

Several studies have examined whether avoidance of aeroallergens results in clinical improvement of AD. Most of these reports have involved uncontrolled trials in which patients were placed in mite-free environments, such as hospital rooms, through the use of acaricides or impermeable mattress covers. Such methods have invariably led to improvement in AD.

One double-blind, placebo-controlled study using a combination of effective mite-reduction measures, as compared to no treatment, in the home showed that a reduction in house dust mites is associated with significant improvement in AD [106].

However, some reports found elimination of mite allergens produced no advantages on AD patients. Oosting [107] reported a double-blind, placebo-controlled study in 2002, which evaluated the effect of mattress encasings on AD outcome. They found that house dust mite-impermeable encasings resulted in a significant decrease in Der p 1 and Der p 1 plus Der f 1 allergen concentrations. However, this reduction in allergen load did not produce significant changes in clinical parameters of AD patients. In a placebo-controlled study, Koopman [108] also reported that house dust mite-impermeable mattress covers on the patients' beds did not improve the symptoms of AD and atopic sensitization in the first 2 years.

Cutaneous Contact Allergens

Contact Dermatitis in AD

Patients with AD are considered by many clinicians to be less prone to sensitization by contact allergens. On the contrary, they are sensitized to common allergens (fragrances, rubber accelerators, lanolin, formaldehyde) as frequently as nonatopic individuals [109, 110]. Recently, there is a tendency for allergy to topical corticosteroid developed in

AD patients. Nonfluorinated corticosteroids especially easily cause contact dermatitis in these patients [111].

Implications for Clinical Practice

Contact dermatitis should be always included in the causes of flare-up in AD. Patch test for common allergens (including topical medications), cosmetic products (emollients), and even corticosteroids should be performed in highly suspected patients with AD and flare-up.

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