

Atopic Dermatitis and Allergen Hypersensitivity: State of the Art

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Abstract: The current growing enthusiasm for atopic dermatitis (AD) is clearly reflected in the range of current attitudes on the subject. What are considered to be its protean manifestations are frequent challenges to the paediatrician and other specialists working with children. AD may occur not only in man, but also in other vertebrates. However, it must be assumed that AD has always been an affection of our species. Hippocrates (460-370 BC) reported urticaria and gastrointestinal upset following cow's milk (CM) ingestion. Lucretius (98-55 BC) wrote that one man's meat is another man's poison. Galen (131- 219) described allergy to goat's milk. At the turn of this century the first description of acute shock due to CM allergy (CMA) and fatal CMA were published. In his pioneer studies of food allergy (FA), Schloss was the first to evaluate skin tests for the diagnosis of FA. Since then, a vast array of symptoms and disorders have been attributed to FA, many of which occur with other conditions. In addition to this, the lack of a single, practical diagnostic test has contributed to the polarization of the scientific controversy between those who believe in and those who deny FA existence. Terminology has also been confusing. A correct use of definitions is necessary for a proper epidemiologic evaluation of the conditions and an accurate diagnostic and therapeutic approach. While this concept was fundamentally correct, it was also too easily weakened by ignoring this prerequisite to be fully acceptable, and this led to an equally disordered use of the term hypersensitivity, since allergy had become a word used to embrace all possible forms of adverse reactions. AD is associated with patchy, characteristically distributed areas of cutaneous eczema, with intense itching and subsequent lichenification of the skin. Cutaneous autonomic dysfunction (increased vasoconstriction) and xerosis (dryness of the skin) commonly occur in the affected children. In addition, profound immunological dysregulation with various immune alterations has been described in affected children. Most children produce IgE antibodies to a number of food and inhalant allergens, at the point that a minuscule offending quantity can trigger a reaction by skin contact or by inhalation.

Keywords: IgE antibodies, allergic inflammation, eosinophils, T lymphocytes, homing receptors, inhalant and food allergens.

INTRODUCTION

Atopic dermatitis (AD) is the main hallmark of the atopic constellation. The disease is most common in infancy and young children and, at present, there is not explanation for this finding. Genetic predisposition is certainly a prerequisite, however a number of environmental factors modulate the phenotypic expression of the disease. Recent data suggests that allergy sensitization and clinical manifestations are genetically determined but the organ specificity of a given allergic disease is acquired, based on environmental factors.

In this paper we will focus on the results of different studies indicating the pathogenic role of allergic sensitization in AD.

IgE IN ATOPIC DERMATITIS

Since the discovery of IgE it has been suggested that these antibodies contribute to the pathogenesis of AD. The role of IgE is based on some evidences: 80-

90% of AD patients have a personal or family history of atopy and serum IgE levels are elevated in about 80-83% of patients with AD [1-4]. In addition, serum IgE levels are highest in patients with coexisting respiratory allergy (rhinitis and/or asthma) and about 85% of patients have positive immediate skin prick tests (SPT) and/or radioallergo-sorbent test (RAST) to a variety of food and inhalant allergens, indicating dysregulation of B cell responses [4, 5].

Substantial evidence supports the notion that elevated serum IgE concentrations highly correlate with disease severity [6]. In addition, 50% to 80% of children with AD have or will present IgE mediated manifestations, such as allergic rhinitis and/or asthma, and food allergy (FA) [5, 7, 8] (Table 1). Nevertheless, there are evidences against an IgE role in AD (Table 2), which are present in several other affections (Table 3). However, further evidences supporting the role of IgE in AD pathogenesis are the studies indicating that inhalant and food allergens can trigger AD, as it will be discussed later.

ALLERGIC INFLAMMATION IN ATOPIC DERMATITIS THE ROLE OF EOSINOPHILS

Recent studies indicate a role for eosinophil disruption and degranulation in inducing tissue

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destruction and several potent, toxic protein in the granules, such as Major Basic Protein (MBP), Eosinophil-Derived Neurotoxin (EDN), Eosinophil Cationic Protein (ECP) and Eosinophil Peroxidase (EPO), are implicated in tissue damage associated with skin inflammation [9, 10]. According with other Authors, we found elevated serum levels of ECP in children with AD, however no correlation between ECP serum levels and total IgE, as well as between ECP serum levels and the absolute number of peripheral blood eosinophils was shown [11]. In addition, ECP has been confirmed to be a sensitive marker of disease activity in AD [12].

Table 1. Evidences Demonstrating a Role of IgE Antibodies in AD

- 1) 70-90% of children have a personal or family history positive for atopic disease;
- 2) Serum IgE levels are elevated in about 80% of patients;
- 3) Serum IgE levels are highest in children with coexisting respiratory allergy;
- 4) About 85% of patients have positive immediate skin tests and/or RAST to a variety of food and inhalant allergens;
- 5) Substantial evidence supports the notion that IgE levels are low during remissions, and higher during flaring of AD;
- 6) 50-80% of children has coexisting allergic IgE-mediated manifestations such as allergic rhinitis and/or asthma, and FA.
- 7) Numerous studies correlate eczematous flares with immediate and/or late-phase skin reactions after SPT and/or patch tests with inhalant and allergens, for example after application of mite extract to the abraded skin of subjects with PTC positive for Der p 1;
- 8) Association between clinical manifestations and food allergens in 30-50% of children; in 33% of subjects undergoing DBPCFC;
- 9) Several reports stress the role of exogenous factors: the removal from potential allergens in their home environment (sea or high altitudes) leads to clearing of eczematous skin lesions;
- 10) Flaring of skin lesions after exposure to environmental allergens and resolution after allergen elimination;
- 11) Reduced prevalence of AD in at risk babies if food allergens are eliminated during the first year of life.

Table 2. Evidences Against a Role of IgE Antibodies in AD

- 1) A marked elevation of serum IgE is found in several diseases, not necessarily atopic;
- 2) About 15-20% of normal children have high concentrations of serum IgE without any clinical manifestation of atopy;
- 3) About 15-20% of children have AD without apparent signs of hyper IgE production;
- 4) IgE synthesis could be secondary to a functional imbalance of the immune mechanisms controlling it;
- 5) IgE antibodies are not a prerequisite for the development of skin lesions, since AD can manifest itself even in not atopic children;
- 6) The typical skin lesion, the pomphus, is not a specific marker of IgE-mediated allergic reaction of AD;
- 7) AD is present in patients with agammaglobulinemia, normal IgE levels, and PTC negative for allergens, as well as in Wiskott Aldrich syndrome

Table 3. Pathologic and Not Pathologic States with an Increase of IgE Levels

AIDS
Addison's disease
Atopic diseases
Bullous pemphigus
Connectivites
Drug-induced interstitial nephritis
Gluten enteropathy
Hepatic cirrhosis
Hyper-IgE syndrome
Infectious diseases
Kawasaki syndrome
Mononucleosis
Myeloma E
Neoplastic diseases
Parasitosis
Periarthritis nodosa
Pulmonary hemosiderosis
Smoking
Wegener granulomatosis
Wiskott-Aldrich syndrome

In patients with AD @,t has been suggested that these proteins are mainly produced locally in the skin and serum EDN seems to be a more sensitive marker of eosinophil degranulation than serum MBP [10]. Interestingly, extensive MBP deposition in the skin was demonstrated in two children who experienced eczematous lesion after double-blind placebo controlled food challenge (DBPCFC), thus confirming the role of FA and eosinophils in AD [10].

Eosinophils have a role in allergic inflammation and interact in cellular networks with antigen-presenting cells, mast cells, and T lymphocytes, which influence eosinophil maturation, mobilization, tissue localization and activation [13].

THE ROLE OF T LYMPHOCYTES

Allergen-specific CD4⁺ T-cells that produce IL-4 but not IFN- γ predominate in the skin lesions and peripheral blood of AD patients suggesting functional impairment of T-cell responses [14, 15]. Interleukin (IL)-4 promotes IgE synthesis and IFN- γ downregulates both IL-4 and allergen-induced IgE production, suggesting that aberrant cytokine production profiles play a central role in the pathogenesis of AD [16]. Recent study, with the use of in situ hybridization to determine the cytokine mRNA (IL-3, IL-4, IL-5, and GM-CSF), has suggested the critical role of these cytokines in modulating the quality of tissue

inflammation [17]. Moreover, initiation of acute skin inflammation is associated with the presence of IL-4 whereas persistence of chronic inflammation is associated with increased IL-5 expression and eosinophil infiltration [18].

Environmental and/or genetic factors may switch the T cells to Th2 phenotype, capable to promote IL-4 dependent IgE synthesis and IL-5 dependent eosinophil differentiation. It has been suggested [19] that the differentiation of Th0 type lymphocytes into Th2 type lymphocyte in AD patients may be related to an abnormality of antigen presenting cells (APC) in target tissue or to intrinsic properties of allergic proteins. In particular, the finding of stimulated atopic leukocytes with elevated phosphodiesterase activity and consequent diminished cyclic adenosine monophosphate levels was correlated to this supposed APC role in directing Th0-Th2 differentiation [20].

Interestingly, Warner *et al.* showed poor production of IFN- α in cord blood mononuclear cells of atopic neonates and this deficiency was predictive of AD development [21]. In addition, Rang *et al.* observed a significantly lower production of IFN- α in neonates who developed either atopic symptoms or a positive IgE-mediated skin prick test at 12 months of age compared with those who did not [22]. Thus, this reduced secretion of IFN- α could enhance the development of atopy by increasing IgE production and/or reducing the ability to clear antigen.

THE ROLE OF HOMING RECEPTORS

Two homing receptors (HR), cutaneous lymphocyte antigen (CLA) and L-selectin, are involved in T-cell migration to skin and peripheral lymph nodes, respectively. It has been demonstrated that T cells migrating into skin have high proportion of CLA expressing memory/effector T cell subset, whereas memory/effector T cells in the asthmatic patient airways are predominantly CLA negative [23]. It has been recently shown that children with cow's milk (CM) induced AD have a greater percentage of cells expressing CLA, but not a higher percentage of T cells expressing L-selectin, in comparison with non atopic subjects [24]. Interestingly, children with CM induced enterocolitis or allergic eosinophilic gastroenteritis do not have such high proportion of CLA⁺ T cells, thus suggesting that the expression of the CLA receptor on antigen-specific T cells may determine the skin symptoms [24].

Since memory/effector T cells usually express HR that lead them to extra-lymphoid tissues, associated with the secondary lymphoid tissues in which they were first activated, the site of allergen exposure may play a role in determining HR expression and the tissue pattern (target organ) of atopic symptoms. Therefore, a child may be prone to develop AD, at the place or before asthma, because of a different skin or lung seeking behavior of his memory/effector T cells [24, 25].

THE ROLE OF INHALANT ALLERGENS

More than 60 years ago, the role of inhalant allergen on AD has been studied, however only recently a number of studies has strongly suggested that even mites can be considered as a triggering factor of AD. In 1930 Cohen described AD patients who experienced eczematous flaring following exposure to ragweed pollen, and more interestingly this author documented with an elegant *in vivo* experiment the rapid absorption of pollen through the respiratory mucosa followed by the transport to the distal skin mast cells [26]. Ragweed pollen was blown into the nostrils of 50 normal control subjects passively sensitized intracutaneously with serum of a ragweed allergic patient and serum of nonatopic controls. Within a mean of 20 minutes all subjects developed a wheal-and-flare response at the sensitized site but not at the control, thus confirming the localization of the pollen in the skin. In several studies pruritus and flares of AD were induced following inhalation of *Alternaria* [27-31]. These inhalation studies of ragweed and *Alternaria* provided the first evidence for a pathogenetic role of aeroallergens in patients with AD.

Several studies of the early '50 have also shown that house dust exposure may influence the clinical outcome of AD. However, it is of note that more than 50 years ago Rost demonstrated that skin lesions remarkably improved when patients with AD were kept in a dust-free environment [32]. Mitchell *et al.* first suggested that the skin lesions of AD could be provoked even by contact with dust mite [33]. Repeated patch test (PT) with aqueous *Dermatophagoides pteronyssinus* (Der p) extract on lightly abraded skin were performed in adult patients with AD. Patients with positive SPTs to Der p had positive PTs at 72 hours epidermal changes, including focal spongiosis and microvesiculation were evident and there was a significant increase in the number of basophils and eosinophils [33]. Biopsy specimen of the positive lesions also showed mononuclear cell and

neutrophil infiltration. Eczematous lesions on not manipulated skin occurred in patients with AD following PTs employing Der p lyophilized commercial preparation [34]. Biopsies of the positive test sites revealed eczematous reaction with epidermal spongiosis and microvesiculation. Immunostaining of cryostat sections showed dermal cell infiltrates consisting of mainly T lymphocytes. Typical AD lesion occurred on non manipulated skin in adults with AD by applying twice a day for 2-5 days an ointment containing *Dermatophagoides farinae* (Der f) [35]. These Authors also demonstrated penetration of Der f (which was linked with ferritin) into the stratum corneum, to epidermis and the dermis. However, the lesions were present only in typical areas and only with previous skin scratch [35]. The Authors hypothesized that AD, rather than being a primary eruption, is likely to be the result of various repeated stimuli, combining reactions including type I and type IV immunoreaction with a primary irritant response to a combination of physical, chemical, and mechanical factors, including scratching due to persistent itching. In fact, following the percutaneous challenge with mite allergen, a type I reaction occurred in the patients. A delayed type IV reaction occurred on repeated challenge [35].

Adinoff *et al.* and Clark *et al.* elicited cutaneous response in patients with AD applying various aeroallergens extracts on clinically uninvolved and not manipulated skin [36-38]. Only patients with positive SPT response to Der p had positive PT response. Norris *et al.* applied, for 5 days, 1 ml of a PT solution containing Der p on the unmanipulated antecubital or popliteal skin of atopic adults with or without AD [39]. Worsening of the skin lesions occurred in 1/3 patients with AD and positive PT response to Der pl. All patients with AD and negative PT to Der p had negative SPT response.

We have studied the PT response to Der p in children with AD, in children who had suffered from AD but the disease was cured, and in atopic children with asthma and without AD [40]. Our data show that a significantly higher proportion of children with AD or who had suffered from AD have positive PT to Der p in comparison to atopic children without AD ($p < 0.001$) [40].

Bruijnzeel-Koomen *et al.* showed 70% positive PT response, applying house dust mite and pollen allergens on the back of AD adult patients, previously removing the superficial stratum corneum by consecutive application of adhesive tape [41]. No

positive responses were found in atopic patients without AD or in controls. These PT cause eczematous lesions. An infiltrate of eosinophils into the dermis was demonstrated, starting 2-6 hours after patch-testing. Immunostaining with antibodies against granular constituents of the eosinophils revealed that infiltrating eosinophils were in an activated state and had lost part of their granular contents. At 24 hours eosinophils also appeared in the epidermis. Histologically, a predominance of T cells of the helper/inducer phenotype have been observed. Electron microscopy showed that some epidermal eosinophils were in close contact with Langerhans cells, thus suggesting a cell-cell interaction. Recent data have confirmed the prevalent role of Der pl in PT lesions, and the close association of the allergen with Th2 lymphocytes [42]. It has been speculated that immediately after PT some allergens penetrate the epidermis, bind the IgE molecules on mast cells in the dermis and induce an immediate type reaction. Mast cell release eosinophil chemotactic factors and some of the infiltrating eosinophils become activated [41]. As already discussed, recent studies demonstrated that in the skin lesions of AD patients' Der pl-specific T clones are Th2 lymphocytes expressing IL-4 and IL-5 and no IFN- γ [42]. On the contrary, in non atopic subjects Der pl-specific T-cell clones produced IFN- γ and only in some cases a minimal amount of IL-4 [43].

Very recently the role of house dust mite in the pathogenesis of AD has been confirmed by a double-blind, placebo-controlled trial on the effect of house dust mite avoidance [44]. This study shows that the activity of AD can be greatly reduced by effective mite avoidance in the domestic environment. In some individuals the amelioration was dramatic, with a substantial improvement in quality of life. The severity of AD decreased both in the active treatment group and in the control group (no active treatment), but the active treatment group showed significantly greater improvement in severity score and area affected from AD [44].

THE ROLE OF FOOD ALLERGENS

The contributing role of food allergens in the pathogenesis of AD has been confirmed by several studies [45-49]. It has been well established by DBPCFC that in at least 36% of children with AD food allergy is a trigger factor [45, 46]. Eggs, peanuts, cow's milk, wheat, fish, and soybean accounted for nearly 90% of the positive reactions in AD patients [45, 48]. The high number of positive skin tests and RAST to

foods found in children with AD supports the frequent observation that children with AD are often allergic to a large variety of foods. However, even if children consume a wide variety of different foods, the most common foods of the Italian diet such as CM, egg and wheat accounted for most of the food hypersensitivity. This finding emphasizes the importance of documenting FA, in order to avoid only the offending food(s) and to prevent nutritional derangement of too restricted diets. However, most of the children with AD (8%) have positive DBPCFC to one or two foods, 15% to three foods and only 3 children to four or more different foods. Thus food-induced AD appears to be rather specific in terms of the number and type of the offending foods. In another study 42% of children with AD aged 6 months-10 years had positive challenge test [49]. Again, cow's milk and egg were the most common offending foods. Employing two foods (CM and egg) for challenges, we have obtained positive reactions in 75% of children, a figure very similar to that of Sampson [49]. Foods frequently reported to induce hypersensitivity such as citrus fruit, chocolate, strawberries, did not elicit positive responses [49, 50]. We have evaluated the efficacy of a CM- and/or egg-free diet in 59 children, aged 2-14 years, suffering from severe AD [5]. The elimination of CM and/or egg for 4 weeks resulted in the healing, or marked improvement of skin lesions in 96% of children.

As regards the allergenicity of soy, we have studied 143 children with a median age of 12 months affected by AD, who had been soy-protein-formula fed for at least 3 months [51]. Only 4/36 children with positive RAST to soy had a positive challenge test to soy. In addition, 2 children with negative RAST to soy had a positive challenge test. Overall only 6/143 children with AD had clinical hypersensitivity to soy.

Release of mediators as a consequence of an IgE reaction, and high levels of serum histamine have been shown in children with AD after a positive DBPCFC response [47].

In conclusion, FA and sensitization to inhalant allergens are important contributing factors of AD. However, it is imperative that each patient should be carefully evaluated with standardised diagnostic procedures to establish whether or not food and/or inhalant hypersensitivity play an important role in the pathogenesis of AD.

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