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Atopic Dermatitis: From Pathophysiology to Diagnostic Approach

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1. Introduction

Atopic eczema/dermatitis syndrome (AEDS) is a chronic inflammatory skin disease, very common in childhood (1). The prevalence of AEDS is estimated to 15–30% in children and 2–10% in adults while the incidence has shown a 2- to 3-fold increase in the past 3 decades in developed countries (2). This results in a significant socio-economic impact, that in the United States was estimated in a range from $364 million to $3.8 billion US dollars per year, usually considering only the direct but not the indirect costs (3). The disease is sustained by a complex interaction between genetic and environmental factors and is characterized by a skin barrier dysfunction resulting in epidermal damage and altered permeability to allergens and microbes (4). Depending on the association or not to IgE sensitization, AEDS may be defined as atopic or nonatopic. The two forms are clinically similar but show some differences regarding the histology, the kind of cells involved, and the cytokine pattern (5).

2. Pathophysiology of AEDS

The pathophysiologic mechanisms leading to AEDS originate from an initial skin defect at epidermal level, above all in the *stratum corneum*, which is the first of the four epidermal layers. The *stratum corneum* (from the Latin words for horned layer) is composed of large, flat cells containing keratin, a protein that helps keep the skin hydrated by preventing water evaporation, and surrounded by lamellae sheets rich in hydrophobic lipids, including ceramides, sphyngosynes and free fatty acids. Keratin is produced by the keratinocytes of the basal layer, which also keep the Langerhans cells and the intradermal lymphocytes in position with the epidermis. They also work to modulate the immune response by secreting cytokines such as TGF-beta and alpha, and a number of interleukins (6). A major advance in the understanding of epidermal barrier dysfunction which occurs in AEDS was the identification of the fundamental role of filaggrin (7). Filaggrin, which derives from the highly phosphorylated polypeptide profilaggrin, the main constituent of the keratohyalin substance in the granular layer, is a structural protein associated to filaments which are bound to keratin fibres in epidermal cells. Recent studies found that loss-of-function mutations in the gene encoding filaggrin, particularly the R501X and 2282de14 mutation, are associated with the development of atopic dermatitis (8-10).

The alteration of the epidermal structure due to filaggrin mutation induces a significant reduction of the lipidic component, particularly of ceramide levels (11) that leads to the well known phenomenon of trans-epidermal water loss (TEWL) resulting in dry skin and itching, while the impaired skin barrier associated with filaggrin deficiency favours the penetration of foreign noxae, especially allergens and microbes (12).

Concerning allergens, it is conceivable that their facilitated access favours the sensitization process, especially for house dust mites, the protease activity of their major allergen being a further enhancing factor (13). Once entered, allergens are captured by dendritic cells (14) that activate an initially local Th2 but a later Th1 response along with a systemic Th2 response inducing the Ig isotype switching to IgE synthesis and the involvement of eosinophils (2). In this kind of response an important factor seems to be thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine expressed by barrier epithelial cells able to activate myeloid-derived dendritic cells, macrophages and mast cells (15). The ongoing inflammatory process is then sustained by the Th2-related cytokine such as IL-5, IL-13, TNF-alpha, IL-17, and IL-31, the latter being primarily expressed in skin-homing Th2 cells (16). An important clinical aspect of the allergen-caused AEDS is the frequent evolution of manifestations to respiratory symptoms such as asthma and rhinitis. This process has been defined as the "atopic march" (17). Also in this case, filaggrin null mutation were found to be associated with the development of asthma (18). However, more than one model of atopic march was reported, because in a significant number of children asthma precedes AEDS as the onset manifestation of the atopic disease (19). Of note, in subjects with AEDS and no filaggrin gene mutations, the cytokines IL-4 and IL-13 (typical of the Th2 profile) are able to inhibit the expression of filaggrin (20). This suggests that if filaggrin deficiency predisposes to atopy, atopy is also likely to impair the filaggrin-dependent skin barrier.

Regarding microbes, the normal skin defence is based on integrity of *stratum corneum* and on immune response by neutrophils and macrophages by production of substances which kill the microbes and by phagocytosis. Numerous antimicrobial peptides produced by keratinocytes and belonging to the classes of beta-defensins and cathelicidins are able to disrupt or penetrate the microbe membrane thus protecting the skin from infections (21). It has been demonstrated that in patients with AEDS there is a deficiency in the expression of beta-defensins and cathelicidins that may account for the susceptibility to skin infection, especially from *Staphilococcus aureus* (22). *S. Aureus* has a major role in AEDS, as indicated by the following features: 1) a very high density of colony-forming units *S. aureus* per cm^2 of inflamed atopic skin lesions (23); 2) the higher affinity for *S. aureus* of the atopic skin compared with nonatopic or psoriatic skin (24); 3) the reduction of *S. aureus* counts on atopic skin sites following effective topical treatment (25). In any form of AEDS, an additional pathophysiologic role is played by the cytokine IL-31 produced by keratinocytes, which exerts a potent pruritogenic effect (26). In fact, pruritus is associated with skin lesions caused by scratching or excessive washing and to consequent damage of keratinocytes and release of mediators, but also of autoantigens, and generation of autoantibodies (27). Moreover, autoreactivity phenomena also concur to pathogenesis of AEDS. In particular, manganese superoxide dismutase (MnSOD) of both human and foreign origin – especially from the long known *Malassezia spp* yeast (28) – may act as autoallergen. Specific IgE against human MnSOD correlating with the disease activity were detected in patients with AEDS, suggesting that human MnSOD with molecular mimicry with MnSOD from *Malassezia* may play a role, as showed by its

capacity to induce in vitro T-cell reactivity and eczematous skin lesions, as an autoallergen in subjects with both atopic and nonatopic forms (29).

3. The allergy tests in diagnosis of AEDS

When food allergens are the cause of AEDS, the commonly used allergy tests, such as skin prick tests and in vitro measurement of specific IgE antibodies, have a role in the diagnostic work-up (30). Concerning food-specific IgE measurement, an useful application was suggested by Sampson and Ho, who identified in a group of 196 children and adolescents with AEDS the food-specific IgE levels predicting a positive result of a double-blind, placebo-controlled food challenge. Such levels, showing a positive predictive value higher than 95%, corresponded to 6 kU/L for egg, 32 kU/L for milk, 15 kU/L for peanut, and 20 kU/L for fish (31). The same author later confirmed the utility of specific IgE concentrations in predicting symptomatic allergy also for other foods such as wheat and soy (32). However, the advances in the knowledge of pathophysiology of AEDS, and particularly the understanding that in this disease the mechanisms of delayed hypersensitivity prevail, suggested the need of new diagnostic tools. The atopy patch test (APT) was recently defined as an important tool in diagnosis of AEDS, because it seems to have a greater significance than skin prick test or RAST, which simply detect the presence of specific IgE antibodies. Thus, allergy tests assessing only the immediate IgE-mediated phase of the allergic response can only partially detect the operating mechanisms. Instead, there is notable evidence supporting the capacity of the APT to reproduce the pathophysiologic events of AEDS.

In biopsy-based studies, a Th2 cytokine pattern was found 24 hours after APT, but a shift to a Th1 pattern, as occurs in chronic AEDS skin lesions, was noted after 48 hours (33, 34). A more frequent positivity to APT was reported in patients with allergen-specific lymphocyte proliferation and expression of activation markers on peripheral blood T-cells following *in vitro* stimulation with house dust mite, cat or grass pollen allergens, than in patients without lymphocyte proliferation (35). Application of the APT to skin of subjects with AEDS was followed by an influx of inflammatory dendritic epidermal cells (36). A significant increase of TEWL was reported in the site of the APT application, both after 48 and 72 hours, compared with the control skin site (37). By immunohistochemical analysis, the presence of IgE on Langerhans cells was demonstrated in positive APT reactions to *Dermatophagoides* in patients with mite-associated AEDS (38).

Clinically, patients with a diagnosis of intrinsic AEDS because of negative IgE tests actually had a positive APT for dust mites (39). This aspect is of particular interest, because AEDS patients with negative SPT and IgE measurement in serum should be defined as nonatopic unless APT is performed. A number of studies evaluated how common such patients are, with different observations. In one study the rate of positive APT in nonatopic patients was 23% (40), while in another study comparing AEDS patients with extrinsic and intrinsic forms, the rate of positive APT was 47.4% and 66.6%, respectively (41). In a European multicenter study, which included 314 patients with AEDS, the frequency of clear-cut positive APT reactions ranged from 39% with dust mites to 9% with celery. A notable observation from the study was that positive APT in face of all SPT and sIgE testing negative was found in 7% of the patients, whereas a positive APT without SPT or sIgE for the respective allergen was seen in 17% of the patients (42). This

lead the authors to conclude that, as no gold standard for aeroallergen provocation in AEDS exists, the relevance of aeroallergens for AEDS may be evaluated by APT in addition to SPT and sIgE. Moreover, in children with respiratory symptoms an exclusive positivity to APT with dust mites was observed (43). On the other hand, it was reported that in 63 children with mite-induced asthma and rhinitis, all with positive SPT and sIgE in serum, 16 (25%) were positive to mite APT too, indicating that delayed hypersensitivity reactions were involved (44).

These observations lead us to investigate the possible factors underlying the positive result of APT in subjects with respiratory symptoms. In our first study, conducted on 297 children (45), we could demonstrate that in patients with asthma or rhinitis a positive APT to dust mite was strongly associated with the presence of current or past AEDS. Instead, most subjects with respiratory disease but a negative history for AEDS had a positive SPT. Multivariate analysis showed that there was a high probability of a positive APT result in patients with AEDS (odds ratio 17.4), in patients with AEDS and respiratory disease (odds ratio 21.9), and in patients with past AEDS and respiratory disease (odds ratio 22.8). These observations were confirmed in a study on a large population of 465 children aged 0.4 to 17.6 years. They were divided into four groups: group A, current AEDS (40 patients); group B, current AEDS with respiratory symptoms (156 patients); group C, past AEDS with respiratory symptoms (203 patients); and the control group, respiratory symptoms with no history of AEDS (66 patients). The APT was significantly more frequently positive in groups with current AEDS (groups A and B) or past AEDS (group C) than in the control group, while SPT and RAST were significantly more frequently positive in the control group (46). Such significant differences in response to APT in patients with diverse clinical expressions suggest that distinctive immunologic mechanisms lie beneath the different manifestations of hypersensitivity to dust mites. It seems conceivable that in subjects with a negative history for AEDS sensitization occurs by respiratory route and leads to the development of a Th2 pattern of response with ongoing production of specific IgE and consequent positive SPT and in vitro IgE tests. By contrast, in the case mite allergens enter through the skin, as it occurs in exposure to common indoor concentrations of the major allergen Der p 1 (47), such entering being facilitated by its proteolytic activity and in the presence of a filaggrin-dependent skin barrier dysfunction, a different chain of events is likely to take place. This is ultimately revealed by positive APT and negative SPT and *in vitro* IgE tests.

The recent observations on the diagnostic significance of APT in patients with different clinical expressions of the disease highlighted the importance of delayed hypersensitivity in AEDS. This brings into question the role of simple IgE sensitization in AEDS and also the appropriateness of the term atopic when applied to AEDS. In fact, current evidence shows that up to two thirds of patients with AEDS are not atopic, therefore even to continue using the term atopic dermatitis is to be considered problematic (48, 49). In fact, the definition of atopy as "a personal or familial tendency to produce IgE antibodies in response to low doses of allergens" (50) seems not to be appropriate for AEDS, as many patients show a positive result to APT but not to IgE tests. At the same time, the definition atopy patch test seems unfounded, because the test does not reveal atopy, i.e. a type I hypersensitivity, but a type IV hypersensitivity according to Gell and Coombs classification (51). A unifying solution should be the use, in both cases, of the term allergy, which is defined as "a hypersensitivity

reaction initiated by immunologic mechanisms" (50) and includes all known mechanisms, as a replacement for atopy.

4. References

[1] Asher MI, Montefort S, Biorksten B, et al; ISAAC Phase Three Study Group Allergies. Worldwide time trends in the prevalence of asthma, rhinoconjunctivitis, and eczema in childood: ISAAC Phase One and Three repeat multicountry cross-sectional surveys. Lancet 2006; 368:733-743.

[2] Leung DY, Bieber T. Atopic dermatitis, Lancet 2003; 361:151-160.

[3] Mancini AJCS, Kaulback K. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. Pediatr Dermatol 2008;25: 1-6.

[4] Boguniewicz M, Leung DYM. Atopic dermatitis. J Allergy Clin Immunol. 2006;117:S475-S480.

[5] Novak N, Bieber T, Leung DYM. Immune mechanisms leading to atopic dermatitis. J Allergy Clin Immunol 2003; 112:S128-S139.

[6] Giustizieri ML, Mascia F, Frezzolini A, et al. Keratinocytes from patients with atopic dermatitis and psoriasis show a distinct chemokine production profile in response to T-cell-derived cytokines. J Allergy Clin Immunol 2001;107:871-7.

[7] Sandilands A, Sutherland C, Irvine AD, McLean WH. Filaggrin in the frontline: role in skin barrier function and disease. J Cell Sci 2009;122:1285-4.

[8] Cookson W. The immunogenetics of asthma and eczema: a new focus on the epithelium. Nat Rev Immunol 2004;4:978-88.

[9] Palmer CN, Irvine AD, Terron-Kwiatkoski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38:441-6.

[10] O'Regan GM, Sandilands A, McLean WHI, Irvine AD. Filaggrin in atopic dermatitis. J Allergy Clin Immunol 2008;122:689-93.

[11] Jungersted JM, Scheer M, Baurecht H, et al. Stratum corneum, skin barrier function and filaggrin mutations in patients with atopic eczema. Allergy 2010;65:911-8.

[12] Leung DYM. Our evolving understanding of the functional role of filaggrin in atopic dermatitis. J Allergy Clin Immunol 2009;124:494-5.

[13] Donnelly S, Dalton JP, Loukas A. Proteases in helminth- and allergen-induced inflammatory responses. Chem Immunol Allergy 2006;90:45-64.

[14] Novak N, Koch S, Allam JP, Bieber T. Dendritic cells: bridging innate and adaptive immunity in atopic dermatitis. J Allergy Clin Immunol 2010:125:50-9.

[15] Corrigan CJ, Jayaratmam A, Wang Y, et al. Early production of thymic stromal lymphopoietin precedes infiltration of dendritic cells expressing its receptor in allergen-induced late-phase cutaneous responses in atopic subjects. Allergy 2010;64:1014-22.

[16] Incorvaia C, Frati F, Verna N, et al. Allergy and the skin. Clin Exp Immunol 2008;153 (suppl 1):27-9.

[17] Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003;112:S128-39.

[18] Palmer CN, Ismail T, Lee TH, et al. Filaggrin null mutations are associated with increased asthma severity in children and young adults. J Allergy Clin Immunol 2007;120:64-8.

[19] Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol 2004;113:925-31.

[20] Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol 2009;124:S7-12.

[21] Nizet V, Ohtake T, Lauth X, et al. Innate antimicrobial peptide protects the skin from invasive bacterial infection. Nature 2001;414:454-7.

[22] Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N Engl J Med 2002;347:1151-60.

[23] Cho SH, Strickland I, Tomkinson A, Fehringer AP, Gelfand EW, Leung FY. Preferential binding of Staphilococcus aureus to skin sites of Th2-mediated inflammation in a murine model. J Invest Dermatol 2001;116:658-63.

[24] Donnelly S, Dalton JP, Loukas A. Proteases in helminth- and allergen-induced inflammatory responses. Chem Immunol Allergy 2006;90:45-64.

[25] Nilsson EJ, Henning CG, Magnusson J. Topical corticosteroids and Staphilococcus aureus in atopic dermatitis. J Am Acad Dermatol 1992;27:29-34.

[26] Sonkoly E, Muller A. Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol 2006;117:411-7.

[27] Terui T. Analysis of the mechanisms for the development of allergic skin inflammation and the application for its treatment: overview of the pathophysiology of atopic dermatitis. J Pharmacol Sci 2009;110:232-6.

[28] Scheynius A, Johansson C, Buentke E, Zargari A, Linder MT. Atopic eczema/dermatitis syndrome and Malassezia. Int Arch Allergy Immunol 2002;127:161-9.

[29] Schmid-Grendelmeier P, Fluckiger S, Disch R, et al. IgE-mediated and T-cell mediated autoimmunity against manganese superoxide dismutase in atopic dermatitis. J Allergy Clin Immunol 2005;115:1068-75.

[30] Caubet JC, Eigenmann PA. Allergic triggers in atopic dermatitis. Immunol Allergy Clin North Am 2010;30:289-307.

[31] Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenge in children and adolescents. J Allergy Clin Immunol 1997;100:444-51.

[32] Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;107:891-6.

[33] Sager N, Feldmann A, Schilling C, Kreitsch P, Neumann C. House dust mite-specific T cells in the skin of subjects with atopic dermatitis: frequency and lymphokine profile in the allergen patch test. J Allergy Clin Immunol 1992;89:801-10.

[34] van Reijsen FC, Bruijnzeel-Koomen CA, Kalthoff FS, et al. Skin-derived aeroallergen-specific T-cell clones of the Th2 phenotype in patients with atopic dermatitis. J Allergy Clin Immunol 1992;90:184-93.

[35] Wistokat-Wulfing A, Schmidt P, Darsow U, Ring J, Kapp A, Werfel T. Atopy patch test reactions are associated with T lymphocyte-mediated allergen-specific immune responses in atopic dermatitis. Clin Exp Allergy 1999;29:513-21.

[36] Kerschenlohr K, Decard S, Przybilla B, Wollenberg A. Atopy patch test reactions show a rapid influx of inflammatory dendritic epidermal cells (IDEC) in extrinsic and intrinsic atopic dermatitis patients. J Allergy Clin Immunol 2003;111:869-74.

[37] Gfesser M, Rakoski J, Ring J. The disturbance of epidermal barrier function in atopy patch test reactions in atopic eczema. Br J Dermatol 1996;135:560-5.

[38] Langeveld-Wildschut EG, Bruijnzel PL, Mudde GC, et al. Clinical and immunologic variables in skin of patients with atopic eczema and either positive or negative atopy patch test reactions. J Allergy Clin Immunol 2000;105:1008-16.

[39] Kerschenlohr K, Decard S, Darsow U, Ollert M, Wollnberg A. Clinical and immunologic reactivity to aeroallergens in "intrinsic" atopic dermatitis patients. J Allergy Clin Immunol 2003;111:195-7.

[40] Seidenari S, Giusti F, Pellacani G, Bertoni L. Frequency and intensity of responses to mite patch tests are lower in nonatopic subjects with respect to patients with atopic dermatitis. Allergy 2003;58:426-9.

[41] Ingordo V, D'Andria G, D'Andria C, Tortora A. Results of atopy patch tests with house dust mites in adults with "intrinsic" and "extrinsic" atopic dermatitis. J Eur Acad Dermatol Venereol 2002;16:450-4.

[42] Darsow U, Laifaoui J, Kerschenlohr K, et al. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. Allergy 2004;59:1318-23.

[43] Fuiano N, Incorvaia C. Comparison of skin prick test and atopy patch test with dust mite extracts in patients with respiratory symptoms or atopic eczema dermatitis syndrome. Allergy 2003;58:828.

[44] Guler N, Kilerleri E, Tamay Z, Ones U. Atopy patch testing in children with asthma and rhinitis symptoms allergic to house dust mite. Pediatr Allergy Immunol 2005;17:346-50.

[45] Fuiano N, Incorvaia C, Prodam F, Procaccini DA, Bona G. Relationship between the atopy patch test and clinical expression of the disease in children with atopic eczema/dermatitis syndrome and respiratory symptoms. Ann Allergy Asthma Immunol 2008;101:174-8.

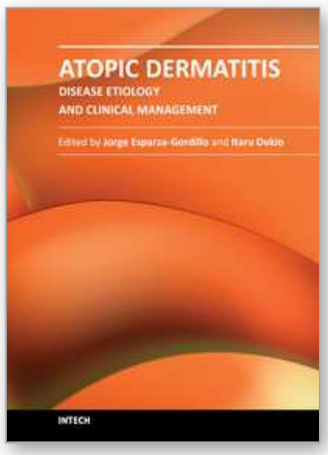
[46] Fuiano N, Fusilli S, Incorvaia C. House dust mite-related allergic diseases: role of the skin prick test, atopy patch test, and RAST in the diagnosis of different manifestations of allergy. Eur J Pediatr 2010;169:819-24.

[47] Huss-Marp J, Eberlein-Koenig B, Breuer K, et al. Influence of short-term exposure to airborne Der p 1 and volatile organic compounds on skin barrier function and dermal blood flow in patients with atopic eczema and healthy individuals. Clin Exp Allergy 2006;36:338-45.

[48] Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis? J Allergy Clin Immunol 2004;114:150-8.

[49] Fuiano N, Incorvaia C. The atopy patch test: is it time to redefine its significance? Ann Allergy Asthma Immunol 2011;106:278-82.

[50] Johansson SGO, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001;56:813-24.
[51] Gell PGH, Coombs RRA, eds. Clinical Aspects of Immunology. 1st ed. Oxford, England: Blackwell 1963.



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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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