

Clinical features and diagnostic criteria of atopic dermatitis in relation to age

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Diagnostic criteria of atopic dermatitis

Chronic inflammatory skin lesions in infancy have been reported for many centuries. The term "atopic dermatitis" was suggested in 1933 by Wise and Sulzberg, to name a skin condition characterised by intense dryness of the skin, pruritus, and chronic erythematous lesions with a relapsing course. Common observations also associated a family history of atopic diseases, involvement of specific body areas and a tendency to resolve spontaneously in early childhood.

The prevalence of AD has been increasing over the last decades. Studies in the first half of the twentieth century have shown an incidence of 2%–3% (1), while more recent surveys have shown an increase to 9%–12% in childhood (2–4). Moreover, similar to other allergic diseases, the prevalence of AD has been found unevenly distributed over the world (5).

The criteria established by Hanifin and Rajka have become the standard for the clinical diagnosis of AD (Table 1) (6). Acute lesions are characterised by erythematous papules, papulovesicles or weeping skin lesions. Subacute lesions reveal erythematous scaling papules and plaques, while chronic lesions consist mainly of lichenification in classically affected body areas. The localisation of the lesions vary with age. In *early infancy* areas mostly involved include the scalp, the face (especially the cheeks and the chin), the trunk

and the extensor surfaces of the extremities. The diaper area as well as the nose is commonly spared in AD. The skin might be highly inflammatory, with large exsudative areas leading to formation of crusts. Lichenification is only rarely observed in early infancy, and itch might not be as debilitating as later in life. Non-erythematous areas are very often characterised by an intense dryness of the skin. Atopic shiners such as Dennie-Morgan infraorbital folds are observed most often in these patients. Infra-auricular fissures are also commonly seen.

In *childhood*, AD is characterised by skin lesions in the flexural areas such as the antecubital and popliteal fossae and the neck, as well as the wrists and the ankles. Lesions of the face are most often not as prominent as in infancy. These localisations tend to persist in *adolescents* and *adults*. Patients in this age range might be especially affected, with lesions involving specific areas such as the perioral or the periocular areas. Frequent topical treatment may affect the skin, e.g. corticosteroid-induced lesions. Furthermore, patients with long-lasting lesions of AD are particularly prone to develop contact dermatitis. Finding the trigger of an acute flare might be especially challenging when an ingredient of topical treatments such as lanolin is involved. Generalised erythrodermia might be observed in a few patients with very severe recurrent lesions.

The histology is mainly non-contributive to the diagnosis, as there are no definite features allowing us to distinguish between AD and other forms of eczema. The acute lesions are characterised by marked intercellular oedema (spongiosis) of the epidermis and a diffuse T-cell infiltrate, suggesting involvement of the immune system in the pathogenesis of the disease (7). In adolescents and adults the histology is that of lichenification, sometimes with an increased number of eosinophils, and with increased numbers of Langerhans cells. Recently it has been shown that there is a sequential activation of T helper 2 (Th2) to Th1 lymphocytes (8). This hypothesis might explain some clinical characteristics of the disease, such as the acute flares clearly related in some patients to contact with allergens, as well as the chronicity of the disease and its relapsing character.

The differential diagnosis of AD is closely related to the age of the patient. In early infancy, AD is most easily confused with *seborrheic dermatitis*. This condition is characterised by onset during the first days or weeks of life, absence of pruritus, involvement of the diaper area, and presence of greasy scaling on a yellow-red base over the scalp, forehead, and nasal folds. The differential diagnosis of seborrheic dermatitis and AD is most often complicated by the seemingly definite seborrheic dermatitis developing into the later condition. Immunodeficiencies with clinical manifestations appearing in infancy or childhood may challenge the diagnosis of AD. The *Wiscott–Aldrich syndrome* is characterised by a mixed humoral and cellular immune disorder associated with a flexural rash indistinguishable from AD. The diagnosis is usually suggested by haemorrhagic diathesis associated with small platelets. Total IgE antibody titres up to several thousand units per ml in AD patients often arouse a differential diagnosis with the *hyper-IgE syndrome*. These patients most often have scalp and face eruptions with fine papular and sometimes pustular skin lesions. The immunodeficiency is suggested by skin and respiratory staphylococcal abscesses, sometimes associated with candidiasis. *Scabies* might be misdiagnosed at any age with AD in presence of highly pruritic, erythematous papular lesions. Similar lesions in other family members indicates this possible diagnosis. Localised lesions should always suggest an eczema related to a *contact allergy*. Nickel might provoke eczematous lesions on specific areas of the body, such as on earlobes after contact with earrings containing nickel, or annular lesions below the umbilicus after contact with jeans buttons. Atopic dermatitis most often first appears in infancy, and exceptionally in

adults. In adult patients, the differential diagnosis should definitely aim to exclude *malignancies* with skin involvement such as Sezary syndrome, Hodgkin's disease or histiocytosis X. A skin biopsy is indicated in these patients.

Common triggers in atopic dermatitis

A clear association between AD and other allergic diseases was recognised early by most clinicians involved in the care of patients with AD, although many dermatologists doubted the allergic component of the disease. Identification of pathogenic factors has been hampered by the complex nature of the disease, as well as by non-specific flare-ups.

Atopic dermatitis is clearly related to an atopic phenotype in most patients. The family history is most often positive, and elevated total IgE antibody levels, or positive specific IgE antibody to common allergens might be observed. Moreover, an inheritance pattern also associating asthma has been identified on chromosome *11q13* (9, 10). The most prominent phenotype is an intense dryness of the skin leading to pruritus. It has been demonstrated elegantly during a positive food challenge in a patient with AD and food allergy that an occluded skin area not reachable for scratching did not flare up (11). Thus, it is mainly intense pruritus and scratching which leads to visible skin lesions. Another major role player in AD is infection. Most patients with AD are colonised with *Staphylococcus aureus*. Active skin lesions are often infected with superantigen-secreting *S. aureus*, with activation of a large number of lymphocytes resulting in intense pruritus (12, 13). The dry lesional skin in patients with AD is easily irritated by a variety of causes, such as wool or nylon fabrics, soaps or topical skin care preparations or sweat. Irritation causes itch, which in turn leads to scratching and initiates the vicious circle of AD flare-up (Fig. 1).

The role of allergy in atopic dermatitis

Among all other factors enumerated above known to influence the natural course of AD, for a long time allergy remained the most controversial. It has long been recognised that foods might in selected patients, exacerbate AD. Several lines of well-established laboratory evidences have been established to link *food allergy* with AD in a subset of patients. Patients with AD have in general elevated total and food-specific IgE antibodies. Also, antigen-activation of IgE molecules leading to mast cell degranulation

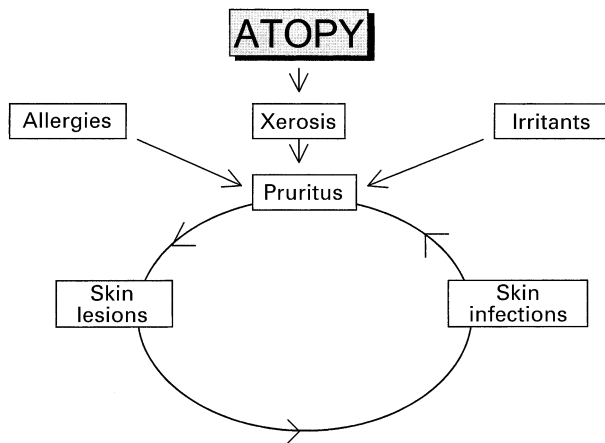


Fig. 1. The vicious circle of atopic dermatitis.

could be found in food allergic individuals with AD (14). In addition, food allergen-specific T cells strongly express a homing receptor specific for the skin (15), and peanut antigen-specific T cells have been cloned from lesional skin (16). Indirect signs of mast cell degranulation have also been observed during positive food challenges with plasma histamine elevation (17).

Numerous clinical observations have addressed the role of food allergy in AD. In 1918, Talbot described a series of patients with AD and positive skin tests to foods who significantly improved after elimination of the suspected foods from their diet (18). More recently, Atherton observed in his series a marked improvement in two-thirds of children with AD during a double-blind cross-over trial of egg and milk exclusion (19). Double-blind, placebo-controlled food challenges (DBPCFC) pro-

gressively became the gold standard in studies examining children with AD suspected with food allergy. A number of reports using DBPCFC have been published by Sampson et al., including over 600 children in more than a decade (20–23). Challenges were performed after an exclusion diet of at least 4 weeks, and in positive challenges cutaneous reactions consisted generally of morbilliform or macular pruritic eruptions in the predilection sites of AD. These reactions were mainly observed within an hour of the beginning of the challenge. Scepticism was expressed by some, due to the rapid apparition of skin symptoms not typically recognised as AD. However, after only few days, continuous feedings elicited the typical skin lesions of AD. Moreover, failure to eliminate the food from the patient's diet prior to the challenge requires a larger amount to provoke the symptoms, which are most often delayed and feature the typical pruritic skin rashes of AD.

Although numerous studies have clearly established a role for food allergy in children, the data are mainly unavailable in adult patients with AD. The early sensitisation to common food allergens and the subsequent loss of sensitivity suggest a much lower number of adult patients with food hypersensitivity (24). Among few reports, an antigen-free, placebo-controlled double-blind diet in adults failed to show a significant improvement in patients on an amino acid formula (25).

Another much-debated issue was raised by the epidemiology of food allergy in AD. Burks et al. diagnosed food allergy in 33% of 46 children with mild to severe AD after positive DBPCFCs (26). In a series of 250 French children with AD, Guillet and Guillet diagnosed an increased number of children with food allergy correlated directly with the severity of the skin lesions (33% of patients with moderate AD, and 93% of patients with severe AD had food allergy) (27). However, patients included in these studies were mostly recruited in allergy clinics, or referred for a suspicion of food allergy, introducing some selection bias. To avoid this potential bias, we evaluated children with AD in two different populations. The first study was conducted at Johns Hopkins University and included patients referred to the pediatric dermatology clinic for primary care of AD (28). Sixty-three children with moderate to severe AD (median age 2.8 years; range 0.4–19.4 years) were evaluated with food-specific IgE antibody and DBPCFCs. Thirty-seven percent were diagnosed with food allergy. Peanuts, followed by egg, cow's milk and wheat, were the foods most frequently involved. The second study was conducted at the University Children's Hospital in Geneva, Switzerland, with a similar study design (29). In this series, 28% of the

Table 1. Major and minor criteria for atopic dermatitis (adapted from Hanifin and Rajka (6, 52, 53))

Major features

- Family history of atopic dermatitis
- Pruritus
- Typical morphology and distribution:
 - involvement of the face or extensor surfaces of the extremities in infancy
 - involvement of the flexor surfaces of the extremities in childhood
- Chronic or relapsing skin lesions

Minor features

- Xerosis/ichthyosis
- Hyperlinear palms
- Increased IgE reactivity
- Hand/foot dermatitis¹
- Chronic scalp lesions
- Periauricular fissures²
- Cheilitis¹
- Susceptibility to cutaneous infections (*S. aureus*, herpes simplex)
- Perifollicular accentuation
- Early age of onset
- Nipple eczema
- Dennie-Morgan infraorbital fold²

¹ Mostly seen in older children and adults; ² mostly seen in infancy.

patients referred to the dermatology clinic were identified with food allergy. Lesions of AD were slightly less severe in these patients, possibly explaining the lower prevalence. Again, egg, milk and peanut were the foods eliciting reactions most often in these patients.

From these studies it is clearly established that approximately one-third of young children with moderate to severe AD suffer from food allergy directly influencing AD. Detection of these patients and identification of the offending foods, mainly by using DBPCFCs, will lead to marked improvement of the morbidity of AD. It should be noted that opposite to a common belief, an adequate restriction diet will improve the skin condition but will not cure the disease. Other triggers may subsist, and the natural course of the disease will not be influenced.

In addition to foods, *other allergens* might be involved in AD. Sensitivity to foods is seen mainly in infants and young children, while older children and adults develop respiratory allergy. Worsening of the skin condition is classically seen in patients with seasonal rhinoconjunctivitis or asthma, mainly on exposed area of the body such as the face or the neck. Among aeroallergens, involvement of dust mites in AD has been well studied. T cells could be isolated, and expanded as T-cell lines or clones after a 24-hour application of allergen on the skin (30). Characterisation of the cells obtained revealed a Th2 phenotype for the majority of the cells. In a clinical study, Wananukul et al. observed positive skin patch tests with dust mite, cockroaches, mould or grasses mixes in 90% of children with AD (31). Guillet and Guillet could incriminate aeroallergens (dust mites, pollens, cat and dog dander) in AD lesions of 12% of children with AD with moderate lesions, and in 40% with severe lesions (27). Involvement of aeroallergens clearly progressed with age, although the implication of aeroallergens was definitely less important than food allergens.

Allergy diagnosis in atopic dermatitis

The mechanisms by which allergens influence the course of AD are clearly in part IgE-dependent. Thus, diagnostic tests will include skin prick testing and the measure of serum specific IgE antibodies. Keeping in mind that not more than approximately one-third of the children with AD will suffer from food allergy, testing will include foods suspected by history, as well as the foods known to elicit reactions most commonly. In western countries, eggs, cow's milk and peanuts account for most of the reactions. Recently, Burks et al. determined that skin prick tests (SPT)

to seven foods (egg, milk, peanut, wheat, soy, fish and cashew) could identify 99% of AD patients with food allergies (32). While negative SPTs most often rule out food allergy with immediate symptoms, the positive predictive value of a positive test is only 30%–50% (33–35). It should be mentioned that in other series either SPT or food-specific IgE remained negative in patients with positive DBPCFCs (36). Whether the quality of the commercial antigen extract influences these results remains to be determined.

Although in general more expensive for screening, *in vitro* testing may provide valuable information for the management of patients with AD suspected with food allergy. Sampson et al. compared the levels of food-specific IgE antibody measured by the Pharmacia CAP System FEIA with the results of DBPCFCs in 196 patients (37). Values predicting a highly likely clinical hypersensitivity (95% positive predictive values) were determined for eggs, milk, peanut and codfish (Table 2). In addition, 95% negative predictive values could be established for most of the tested allergens. The "grey zone" of food-specific IgE antibody titres between the 95% positive predictive value and the 95% negative predictive may indicate the presence of food-specific IgE antibodies without clinical hypersensitivity, or suggest food hypersensitivity. Such patients should be evaluated by standardised food challenges, representing the gold standard for the diagnosis of food allergy.

In addition to foods, routine testing may include house dust mites and grasses. House dust mites avoidance measures may significantly improve the disease in sensitised patients. In addition, young children already sensitised with house dust mites or grasses may benefit from a preventive therapy for development of asthma later in life (38, 39).

The role of allergens in the delayed phase of AD might be missed when investigation relies exclusively on SPTs or antigen-specific IgE tests. Atopy patch tests (APT) have been developed as an experimental model and a diagnostic tool. Several

Table 2. Positive predictive Pharmacia CAP System FEIA values (PPV) and negative predictive CAP values (NPV) to specific foods in the diagnosis of food allergy (95% PPV or 95% NPV unless specified). All CAP values in UI/ml (adapted from Sampson and Ho (37))

Food	NPV	PPV
Milk	0.8	32
Egg	0.6 (90% NPV)	6
Peanut	<0.35 (85% NPV)	15
Wheat	5	>100 (75% PPV)
Fish	0.9	20
Soy	2	65 (50% PPV)

authors could demonstrate recruitment of inflammatory cells involved in AD by APTs (40, 41). In addition, delayed-type reactions to various antigens could be correlated to positive APTs. The specificity of APTs was found higher for testing with dust mite antigen, cat dander and grass pollen (between 69% and 92%) than for SPT or specific IgE antibody testing (42). The same group of investigators correlated positive APTs to grass pollens with eczema flares during the pollen season (43). However, APTs may only reflect sensitisation to an aeroallergen, without clinical correlation (44). Similar to aeroallergens, positive APTs to foods could be correlated with positive food challenges, and in particular with late-phase reactions (45). A combination of both SPT and APT may significantly enhance the accuracy of diagnostic procedures, as was demonstrated elegantly by Isolauri et al. (46).

Standardised food challenges, and in particular DBPCFC, are needed for accurate diagnosis in any patient with a history of a possible reaction to a food, improvement of AD after an appropriate elimination diet, and a diagnostic test not allowing to clearly rule out or diagnose food allergy. These procedures have been used extensively in clinical studies and in allergy practice and are well established (47, 48). They should only be performed by well-trained physicians in medical settings allowing management of anaphylactic reactions. Furthermore, patients with a recent history of a severe reaction should not be challenged. The test is usually conducted after a 4-week elimination diet, and consists of two challenges, one containing the test food hidden in a vehicle camouflaging the taste, the odour and the colour, and one containing a placebo hidden in the same preparation.

Natural history

Atopic dermatitis occurs typically in relation to the age of the patient. Within the "atopic march", AD is usually the first manifestation of the atopic phenotype. While most patients develop their first skin lesions before the age of 10 years, they also frequently "outgrow" AD within the first years of life, although a tendency to keep a dry skin subsists throughout life. Unfortunately, allergic asthma often develops in childhood in the patients with a strong atopic phenotype. Allergen avoidance measures involving food-allergen avoidance diets and environmental control may partially influence this seemingly ineluctable allergic progression (49–51). Adults suffering from AD with initial onset in infancy or childhood probably represent a group of atopics with a strong "cutaneous phenotype".

Unfortunately, our current understanding of the disease allows us to control skin inflammation, to detect and eliminate contributory allergic triggers, but does not provide an effective tool to stop the progression of the atopic phenotype from skin to respiratory organs, and from childhood to adults.

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