Classification, Clinical Features and Differential Diagnostics of Atopic Dermatitis

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Classification of Atopic Dermatitis

Classification by Means of Allergic Sensitization

Atopic dermatitis (AD) is characterized by severe pruritus, a chronically relapsing course, a distinctive distribution of eczematous skin lesions, and a personal or family history of atopic diseases. It often begins in early infancy and follows a course of remissions and exacerbations. The role of exogenous and endogenous factors in the pathophysiology of AD has been intensively discussed in recent years. There is increasing evidence that T cell responses to environmental or food allergens are important for the pathogenesis of AD. In patients with AD, the skin disease is most often associated with the existence of environmental or food allergen-specific IgE. This variant of the disease, which is also associated with environmental allergen-specific IgE, is usually called the ‘extrinsic’ form of AD. The ‘intrinsic’ variant is found in 20% of diseases with the typical clinical appearance of AD but without specific IgE [1].

In this respect, AD resembles bronchial asthma: Indeed, this dichotomy of extrinsic versus intrinsic was first used for asthma. The terminology of extrinsic or allergic asthma was first introduced by Rackeman in 1947 and referred to the triggering role of allergens in asthma. As intrinsic asthmatic patients appeared not to be improved by conventional treatments, Rackeman considered intrinsic asthma to be caused by a nonallergic, unknown phenomenon [2].

The concept of extrinsic and intrinsic types was adopted by Brunello Wüthrich, Zürich, Switzerland in the 1980s [3]. Authors from The Netherlands denominate the intrinsic variant also atopiform dermatitis [4]. According to an EAACI nomenclature
task force, the term ‘atopic eczema/dermatitis syndrome (AEDS)’ was proposed to be used to cover the different subtypes of AD. In this nomenclature, the intrinsic type was termed nonallergic AEDS, which shows normal IgE levels, no specific IgE, no association with respiratory diseases (bronchial asthma or allergic rhinitis), and negative skin-prick tests to common aeroallergens or food allergens [5]. However, the classification into extrinsic AD and intrinsic AD has been most widely used during the last years. Perhaps the old term ‘neurodermatitis’ should be reintroduced to differentiate the intrinsic form from AD associated with specific IgE to food or inhalant allergens (table 1).

**Classification of Atopic Dermatitis by Genetic Factors and Phenotypes**

It appears that more different disease mechanisms than IgE-mediated sensitizations are important for different subgroups of patients suffering from AD. This is reflected by the fact that a multifactorial trait involving numerous gene loci on different chromosomes (3, 5 and 11) have been observed. Described genetic polymorphisms in AD involve mediators of atopic inflammation on different chromosomes, some of these may also play a role in respiratory atopy [6]. By means of genetic differences, different classification schemes may be developed.

One group of involved genes with mutations or polymorphism detected in subgroups of patients with AD is related to skin barrier: high associations have been

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**Table 1. Characteristics of intrinsic AD (summarized by Tokura [18])**

<table>
<thead>
<tr>
<th>Serological findings</th>
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<tbody>
<tr>
<td>Normal total serum IgE values (mean total serum IgE, 22.2–134 kU/l)</td>
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<tr>
<td>Absence of specific IgE for environmental allergens and food allergens</td>
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<tr>
<td><strong>Female predominance (collectively 70–80%)</strong></td>
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<tr>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td>No ichthyosis vulgaris or palmar hyperlinearity</td>
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<tr>
<td>No nonspecific hand or foot eczema</td>
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<tr>
<td>Lower colonization of <em>S. aureus</em></td>
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<tr>
<td>Relatively late onset</td>
</tr>
<tr>
<td>Milder severity</td>
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<tr>
<td><strong>Skin barrier</strong></td>
</tr>
<tr>
<td>Normal barrier function</td>
</tr>
<tr>
<td>No filaggrin mutation</td>
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<tr>
<td><strong>Immunological features</strong></td>
</tr>
<tr>
<td>Lower expression of IL-4, IL-5, and IL-13</td>
</tr>
<tr>
<td>Higher expression of IFN-γ</td>
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<td><strong>High prevalence of metal allergy</strong></td>
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shown with mutations in the filaggrin gene also associated with ichthyosis vulgaris, highlighting the predisposing barrier defect in AD patients. That means that for a substantial part of patients abnormal skin barrier function (‘dry’ skin) due to abnormal lipid metabolism and/or epidermal structural protein formation (e.g. filaggrin loss-of-function mutations, protease inhibitor deficiency) may be relevant for the initiation of the disease. On the other hand, there may be a smaller subgroup of patients with AD not suffering from dry skin [7, 8].

Other pathologic factors of innate immunity may lead to abnormal microbial colonization with pathogenic organisms such as *Staphylococcus aureus* or *Malassezia furfur* (compared to *Staphylococcus epidermidis* in normal individuals) and subsequent increased susceptibility to skin infection [9]. Some of the innate immune defects observed in AD are primary defects such as defects in signaling or expression of innate receptors (e.g. TLR2, NOD2). Others may be secondary to the effects of the adaptive immune response. For example, deficiencies in antimicrobial peptides may be due to the overexpression of Th2 cytokines such as IL-4 and IL-13 in acute eczema.

A number of immune deviations in the adaptive immune system have been described – these may in part be associated rather with the so-called extrinsic variant of AD: Like in other atopic diseases there is a general overexpression of Th2 cytokines in many patients with AD. Polymorphisms in IL-4, IL-5, IL-13 and the IL-4R have been described for patients with AD in numerous publications [6].

Th2-associated molecules are closely linked to the regulation of IgE which is higher than normal in 80% of all patients. Specific IgE is commonly associated with food or environmental allergens. Antigen-bearing dendritic cells, binding IgE mainly via the high-affinity Fc receptor FcεRI, are present in the epidermis and mainly in the dermis in AD. Polymorphisms of this receptor have been described as well for subgroups of AD patients. Binding of allergens to Fc receptors of those cells is thought to facilitate antigen presentation to specific T cells [8].

T cells, many of them expressing the skin homing molecule cutaneous lymphocyte antigen, have been identified in the circulation and in the skin in AD. More recent studies point to the fact that specific immune responses including T lymphocytes and specific IgE are directed against autoantigens and microbial antigens as well [9, 10]. Those antigens/allergens may be directly involved in the eczematous skin reaction and may lead to chronic courses (autoantigens) or clinical phenotypes (e.g. head and neck dermatitis and malasezia antigens).

Eczematous patch-test reactions to house dust mites, pollen, animal dander, or foods are frequently observed in sensitized patients. These tests have helped to understand the pathophysiological role of different hematopoietic cell populations in the early eczematous reaction. In the acute phase of eczema, the majority of T cells express Th2 cytokines (IL-4, IL-13, and the novel itch-inducing Th2 cytokine IL-31). During chronification, the Th1 cytokine IFN-γ is increased in the skin. More recently, it became clear that IL-17 and IL-22, two T cell cytokines acting on constitutive
epithelial cells are also secreted into the skin of AD patients. It may be envisioned that a polymorphism in the regulation of these cytokines may lead to novel classifications and therapeutic approaches to AD in the future [11, 12].

Clinical Features of Atopic Dermatitis

The highest incidence of AD is found within the first 2 years of life although the disease can begin virtually at any age [13]. A small proportion of patients present with AD before the age of 6 months and, in this situation, it is important to exclude the common dermatologic problem of infantile seborrheic dermatitis usually involving the napkin area (in contrast to AD). In the young infant the trunk, cheeks, and the extensor sites of the extremities are frequently involved and as the infant develops the limbs also become affected.

Many infants with AD have erythematous oozing lesions, predominantly on the cheeks. As the child grows, the affected sites tend to be the hands, the neck area, and the feet. The older child has predominant involvement behind the knees, in the elbow folds, and frequently also on the face. The adult patient has a more generalized distribution, commonly with diffuse involvement on the trunk and upper thigh area.

Many patients present subacute eczema in clinical practice (fig. 1a) and with continual rubbing and excoriation, the skin becomes lichenified and develops a thickened, coarse appearance (fig. 1b). A clinical variant found in adolescents and adults is the pruriginous form of AD, which is probably caused by repeated localized scratching (fig. 1c).

The facial appearance of a patient with chronic AD is characteristic, with premature small wrinkles underneath both eyes – Dennie-Morgan folds – and, frequently, the loss of the outer third of the eyebrow through rubbing the face on the pillow while sleeping. This is referred to as Hertoghe’s sign. The characteristic white dermographism of the atopic patient gives rise to an unhealthy pallor.

Young women with AD may develop persistent and, at times, severe dermatitis around the nipple and periareolar area.

In a proportion of patients with hand dermatitis their condition is associated with atopy. This should be considered particularly with regard to hairdressers, nurses, and others whose work involves persistent exposure of the skin to detergents, soaps and other degreasing materials. A large proportion of patients with chronic AD have an associated dry skin, which is frequently hypersensitive and mildly pruritic, and its control may help to alleviate the pruritus of AD.

Some patients with AD do not develop their first lesions until later childhood, adolescence, or even adulthood.

The diagnosis of AD is usually made by evaluation of anamnestic data and clinical presentation. According to Hanifin and Rajka [14], three of their major and three of their minor criteria (table 2) must be fulfilled to classify a skin disease as AD. Since this list is too long to be evaluated in daily practice, easier diagnostic criteria have been subsequently defined. The UK working group on AD
Fig. 1. Different features of atopic dermatitis. 

a Subacute dermatitis. b Chronic dermatitis with lichenification. c Pruriginous nodules in AD. d Acute oozing dermatitis.
displayed a simplified proposal, which was evaluated by a multicenter study group later (table 3) [15].

Laboratory data may sometimes be helpful in the diagnosis and classification of AD. Patients with AD frequently have eosinophilia and approximately 80% of patients have abnormally high serum levels of IgE, the highest levels being recorded in those patients with additional respiratory symptoms and in those with apparently associated food allergy. However, up to 15% of the normal population have serum IgE levels above the normal range and a number of other diseases (e.g. helminthic infestations, cutaneous T cell lymphoma) are also associated with high serum IgE levels. Thus, total serum IgE levels are not specific markers of the AD patient.

In vitro or skin prick tests to identify IgE levels specific to allergens have a higher specificity in the diagnosis of atopy than total serum IgE. In the young child, the bulk of IgE is directed against ingested foodstuffs; however, later in life, a large proportion of IgE appears to be directed against inhalant allergens. It is important to note that these tests show a sensitization but often do not prove that the patient has a clinically relevant allergy [16].

Patients with AD are unusually susceptible to cutaneous viral infections: patients with AD have a higher than expected incidence of warts caused by human papilloma

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**Table 2.** Diagnostic criteria of AD according to Hanifin and Rajka [14]: guidelines for the diagnosis of AD

*Major features (at least three must be fulfilled)*

- Pruritus
- Typical morphology and distribution: flexural lichenification or linearity in adults, facial and extensor involvement in infants and children
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, AD)

**Table 3.** Diagnostic criteria of AD according to the UK Working Party’s diagnostic criteria for AD

- Itchy skin condition (obligatory)

*Plus three of more of the following*

- History of flexural involvement
- History of asthma/hay fever
- History of generalized dry skin
- Onset of rash under the age of 2 years
- Visible flexural dermatitis

According to Williams et al. [15].