Development of new treatment modalities for atopic dermatitis
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The millennium criteria for the diagnosis of atopic dermatitis

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SUMMARY

Atopic dermatitis forms an active area of basic and clinical research, where important new knowledge about genetics and immunopathogenesis has surfaced over the past years, and where simultaneous development of new and innovative therapies is under way. However, the inclusion of any patient in an atopic dermatitis study, whether it is on its genetics, pathogenesis or therapy, requires a diagnosis which is irrefutable. Since there is no simple and also no complicated laboratory procedure to reach a diagnosis of atopic dermatitis, different sets of clinical criteria have been developed for the purpose of making the diagnosis uniformly in different studies as well as in different study centers. The most commonly used are Hanifin and Rajka's set of diagnostic features, which have major and minor clinical criteria to be fulfilled in order to establish a diagnosis of atopic dermatitis. Recent developments in the immunology of atopy have clearly established the major abnormality in this syndrome, the preferential production of allergen-specific IgE. In this contribution, it is suggested that the presence of such antibodies in a given patient should be a mandatory criterium for the diagnosis of atopic dermatitis. Such a diagnostic test however establishes a diagnosis of atopic syndrome, not atopic dermatitis. Thus, for atopic dermatitis we have to rely, for the time being, on additional clinical criteria. The clinical features described in the literature are critically evaluated, and it is suggested that in addition to the mandatory presence of allergen-specific IgE, 2 of 3 principal criteria (pruritus, typical morphology and distribution, chronic or chronically relapsing) should be present for such a diagnosis. Finally, the minor features originally described by Hanifin and Rajka and later evaluated by others are revised and divided over 4 subcategories; a) related to subclinical eczema; b) related to dry skin; c) extra skin folds; and d) ophthalmological pathology. They are suggested to be used as additional criteria only, needed when clinical suspicion is high but the new mandatory and principal diagnostic criteria described here are inconclusive. For study purposes, we suggest that the mandatory and principal criteria are sufficient. They are now evaluated and validated in ongoing atopic dermatitis treatment studies.
INTRODUCTION

The pathogenesis, diagnosis and therapy of atopic dermatitis form major area’s of continuing investigation. There is however a general lack of consensus about the disease’s definition, background, diagnosis and therapy. The complexity of atopy is indeed confounding in all these categories of scientific attention. How can we study pathogenesis (including genetics) and treatment of a disease if the diagnosis is still a matter of debate? Which patients are we to include in such studies? In relation to pathogenesis, there is a serious controversy in that some investigators believe the dermatitis is the result of a genetically determined disturbance of lipid metabolism in cell membranes (1), while others see it primarily as an immunological disorder (2). The diagnosis is made on the basis of clinical experience. Therapeutic measures, especially in the area of allergen elimination, lack consensus. Further research is impeded by this lack of agreement in the fields of atopic dermatitis pathogenesis, diagnosis and therapy.

With respect to diagnostic criteria, Hanifin & Rajka were among the first (in 1980) to formulate a set of diagnostic features, reflecting the outcome of discussions held during the International Symposium on Atopic Dermatitis, that was organized in Oslo, June 7-9, 1979 (3). They defined atopic dermatitis to be present when a patient fulfilled 3 of 4 major criteria as well as 3 of 23 minor criteria (Table I). In practice, these criteria are not routinely used but in (patho)genetic, epidemiological and clinical studies, they are widely applied, thereby minimizing patient selection bias in the outcome of such investigations. An opposing and simple diagnostic couple of criteria was suggested by Krafchik (oral communication), who identifies childhood atopic eczema when there is the presence of eczema of the cheeks as well as xerosis. Consensus about diagnostic sets of criteria is clearly absent.

Since Hanifin & Rajka published their diagnostic criteria, new knowledge as to the pathogenesis of atopy in general as well as of atopic dermatitis in particular has emerged. This should have implications for the diagnostic features. Also, several groups have tried to use statistical techniques and validation systems to evaluate the diagnostic features originally described by Hanifin and Rajka. It is appropriate to include new knowledge about pathogenesis as well as these evaluations of diagnostic features into a new set of adjusted criteria, to be called the millennium criteria for the diagnosis of atopic dermatitis.
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Table 1: Diagnostic features of atopic dermatitis as defined by Hanifin & Rajka (3)

**Major features (3 of 4 present)**
- pruritus
- typical morphology and distribution of skin lesions
- chronic or chronically relapsing dermatitis
- personal or family history of atopy

**Minor features (3 of 23 present)**
- xerosis
- ichthyosis / palmar hyperlinearity / keratosis pilaris
- immediate (type I) skin test reactivity
- elevated serum IgE
- early age of onset
- tendency towards cutaneous infections / impaired cell-mediated immunity
- tendency towards non-specific hand or foot dermatitis
- nipple eczema
- cheilitis
- recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- keratoconus
- anterior subcapsular cataracts
- orbital darkening
- facial pallor / erythema
- pityriasis alba
- anterior neck folds
- itch when sweating
- intolerance to wool and lipid solvents
- perifollicular accentuation
- food intolerance
- course influenced by environmental / emotional factors
- white dermographism / delayed blanch
Pathogenesis of atopic dermatitis

Atopy is an inheritable syndrome. Patients with the atopic syndrome may develop atopic dermatitis, allergic contact urticaria, dyshidrotic eczema, allergic rhinitis, allergic asthma, allergic conjunctivitis, gastrointestinal allergy or any combination of these clinical entities. Genes responsible for this syndrome are now being identified. It is expected that in addition to genes responsible for the abnormalities shared by all atopy patients, other genes must be related to the particular organ expression of atopy in a given patient. Interestingly, atopic dermatitis patients were found to have a polymorphism in the gene coding for mast cell chymase, a gene only expressed in cutaneous mast cells (4). Other genes implicated thus far in the genetics of atopy include those responsible for alternative forms of the β chain of the high affinity receptor for IgE (FcεRIβ) (5), where RsaI polymorphisms were found to be highly associated with atopic dermatitis but also with asthma (6).

Atopy is characterized by allergen-specific IgE production (7). The basis of this is skewing of T cells specific for allergenic epitopes. Patients with the atopy syndrome have an abnormality at the level of Th1/Th2 regulation (8). Preferential outgrowth of Th2-like cells, also known as skewing or polarizing, upon allergenic challenge leads to Th2 specific cytokine production. Most recently, an association was found between atopy and a ‘gain-of-function’ mutation in the α subunit of the interleukin-4 receptor (9). IL-4 activates its receptor on B-cells, triggering them to produce IgE. Also, enhanced IL-4 receptor function might lead to enhanced expression of adhesion molecules on endothelial cells for eosinophils influx. Finally, enhanced IL-4 receptor function may lead to preferential outgrowth of CD4+ type 2 T helper cells, which then produce additional IL-4.

The Th2-like cytokine profile (IL-4, IL-5, IL-13) thus stimulates IgE production by B-cells and the plasma cells derived from them. It must be emphasized that this selective Th2-outgrowth and stimulation of IgE-production occurs in the lymphoid organs. It does not occur in the uninvolved or involved skin of atopic dermatitis patients, since B- or plasma cells are not present there. It is also important to realize that it is not known whether this skewing occurs early in life, and subsequently becomes irreversible, or that it is a continuous process.

The allergen-specific IgE molecules so produced enter the circulation and ‘sensitize’ the organs involved in atopy, by binding to mast cells and dendritic cells through IgE-receptors on these cells (FcεRI). Subsequent reintroduction of allergens in these organs may then lead to a variety of local immune responses after binding to cell-bound allergen-specific IgE. In atopic dermatitis, it is believed that allergen binding by IgE on dendritic cell membranes leads to
antigen focusing in situ, enabling T-cell responses to develop in the skin after introducing minute amounts of allergenic peptides.

One of the remaining puzzles in atopy is the observed restriction of these skewed Th2 responses towards a limited set of environmental antigens. Atopy patients make IgE antibodies to a wide variety of aeroallergens and to food allergens, but not to any (glyco)protein derived peptide they encounter. There is as yet no reasonable explanation for this restriction, but is important to realize this for clinical purposes. Detection of allergen-specific IgE is limited to panels of allergens to which atopics are known to respond.

**Application of new immunological knowledge of atopy pathogenesis:**

**Definition of a new and mandatory criterium**

Since production of allergen-specific IgE is such a central abnormality in atopic syndrome, it should be a prerequisite for the diagnosis of atopy in general and atopic dermatitis in particular. Therefore, we suggest to introduce a mandatory criterium for the diagnosis of atopy as well as for the diagnosis of atopic dermatitis, the presence of allergen-specific IgE. Theoretically, one might want to look for allergen-specific IgE where it is produced, i.e. in the lymphoid tissues. Of course, this is no option. Practically, allergen-specific IgE may be traced in the circulation by using a radio-immunoassay or ELISA on patient serum. Alternatively, allergen-specific IgE may be traced in the skin, where it is bound to cutaneous mast cells via FcεRI receptors. Intracutaneous challenge with allergens will lead to immediate, mast cell mediated responses of erythema, urtica and sometimes bulla formation. The panel of allergens used in in vitro as well as in vivo assays should be chosen in such a way that they will cover as much atopics as possible. A reasonable panel would be consisting of housedust mite allergens, mixture of pollens, mixture of fungi, mixture of animal dander, and mixture of food allergens.

The presence of allergen-specific IgE may be actual or historical. If such testing has been performed previously, for example for asthma, the results do not need to be repeated. If such testing is impossible, such as in very young children, one might consider to make a presumptive diagnosis of constitutional eczema, to be confirmed at a later stage as being atopic dermatitis. Such an approach would also be applicable to very young children in whom allergen-specific IgE can as yet not be detected with present technology: titers of allergen-specific IgE will rise and will be detectable at a later stage. Finally, efforts might be directed, when allergen-specific IgE cannot be detected with the screen mentioned, at identifying allergen-specific IgE towards less common allergens. In the future, one might expect that this mandatory criterium for the diagnosis of atopy will be replaced by gene technology, through which the
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responsible genes for atopy are identified in a given patient (gene fingerprinting).

A major issue then is what to do with patients who fulfill the principal criteria to be described below, but in whom allergen-specific IgE cannot be detected, also not at repeated occasions. In these cases, a number of diagnoses in which atopic dermatitis-like symptoms may occur, such as Wiskott-Aldrich syndrome, hyper-IgE syndrome and others, should be excluded. If they are excluded, we suggest to diagnose these patients as having constitutional eczema, without referring to atopy. Some investigators prefer to use intrinsic atopic dermatitis for these cases, but we prefer for reasons described here that it is better to avoid the word atopy, and therefore we prefer the term constitutional eczema.

Principal criteria

In a given patient, the presence of allergen-specific IgE will identify him or her as having the atopic syndrome. The next thing necessary for a diagnosis of atopic dermatitis obviously is the presence of typical skin symptoms. Here we have to rely again on clinical criteria and it is reasonable to take the major features of Hanifin and Rajka as a lead. If we refer to their original major features (Table 1), the item of a personal or family history of atopy can be deleted, because it is a mandatory criterium that a patient has allergen-specific IgE, thus is having atopic syndrome, whether familial or not.

Of the 3 remaining major features (pruritus, typical morphology and distribution, chronic or chronically relapsing), the presence of 2 would be essential to make a diagnosis of atopic dermatitis (Table 2). Thus, we suggest that in addition to the mandatory criterium, patients should fulfill 2 of 3 principal criteria to enable a diagnosis of atopic dermatitis.

With respect to the criterium of typical morphology and distribution, it must be emphasized that if a patient does not have the typical age-related distribution and morphology of skin lesions, another dermatological entity should be excluded. For example, dyshidrotic eczema in a patient with atopy would fit in these criteria (allergen-specific IgE present, pruritus, chronically relapsing), but is excluded because it is another clinical entity, although related to atopy. Occasionally, metal allergy may mimic the clinical picture of atopic dermatitis and when possible, it should be excluded.

One might argue that all 3 remaining principal features, as defined here, should be mandatory criteria as well, but it should be considered that there are patients who do not fulfill all three of them simultaneously, but certainly have atopic dermatitis. For example, the distribution may sometimes not be entirely typical, such as on extensor surfaces of the extremities (atypic atopic dermatitis). Pruritus is almost always present, but there are rare exceptions. And
finally, some patients may have only a very limited period in their lives with atopic dermatitis; they are not chronic or chronically relapsing, and would thus not fulfill the new diagnostic criteria. Thus, 2 of 3 and not all 3 of the principal criteria must be fulfilled.

**Table 2 The millennium criteria for the diagnosis of atopic dermatitis**

- **1- mandatory criterium**
  - presence of allergen-specific IgE:
    - historical, actual, or expected (in very young children)
    - in peripheral blood (RAST, ELISA) or in skin (intracutaneous challenge)

- **2- principal criteria (2 of 3 present)**
  - typical distribution and morphology of eczema lesions:
    - infant, childhood, or adult type
    - if distribution is not typical, exclude other entity
      (dyshidrotic eczema, contact dermatitis, contact urticaria)
  - pruritus
  - chronic or chronically relapsing course

**Evaluation of minor criteria**

Several groups have tried to evaluate the significance of minor features in relation to their occurrence or presence in control groups. Svensson et al (10) developed a new diagnostic tool for the diagnosis of atopic dermatitis, using various statistical methods after collecting data on the historical or actual presence of major and minor features in atopic dermatitis patients and in control subjects. Although their work is not primarily focused on establishing the actual significance of each feature, their data might allow the exclusion of a number of minor features from the original list proposed by Hanifin and Rajka. These include nipple eczema, cheilitis, anterior neck folds, keratoconus, and white dermographism / delayed blanch, which all occurred in control subjects, without statistical difference from their presence in atopic dermatitis patients.

Mevorah et al (11) also studied the significance of 8 minor criteria (nipple eczema, cheilitis, Dennie-Morgan infraorbital fold, pityriasis alba, anterior neck folds, wool intolerance, white dermographism and infra-auricular fissuring). They could not detect statistical significance as compared to a control group for 2 of these 8; Dennie-Morgan infraorbital fold and anterior neck folds. Nagaraja et al (12) studied the original minor features for their significance in a group of 100 childhood atopic dermatitis patients, compared to a control group of 100
children. Eight features were found to be non-specific; ichthyosis, nipple eczema, cheilitis, keratoconus, anterior subcapsular cataracts, and food intolerance.

Rudzki et al (13) also studied the significance of minor features in atopic dermatitis. All the minor features that one might want to erase from the list based on the work of Svensson et al (10), Mevorah et al (11), and Nagaraja et al (12), however, were found to be significantly more common in atopic eczema patients than in control subjects. Diepgen et al (14) also addressed the issue, adding a number of minor features such as photophobia, Hertoghe sign (thinning or complete absence of the eyebrows in the lateral aspects), cradle cap (scaling and crusting of the scalp during infancy), auricular rhabades, and perlèche. Nagaraja et al (12) also had added diffuse scaling of the scalp and infra-auricular fissures, confirming earlier studies of Kanwar et al (15) and Tada et al (16). Diepgen et al (14), similar to Rudzki et al (13), could not omit any of the minor features on the basis of their statistical evaluations. Finally, some features change in their relevance over time, as summarized by Rothe and Grant-Kels (17).

Modification of minor criteria into additional criteria
Hanifin & Rajka introduced their concept of minor criteria, of which 3 should be present (Table 1), to “allow exclusion of, for example, a patient with chronic allergic contact dermatitis who has pruritus, lichenification and family history of atopy” (3). However, such a patient would not be classified as atopic dermatitis in the present modified criteria, because he has another dermatological entity that should be excluded (Table 2). We believe that with the new set of mandatory and principal criteria, a diagnosis of atopic dermatitis can be made. The minor are not necessarily any more for this purpose. However, in cases of doubt, the minor criteria may be of help, and thus they need to be critically evaluated in relation to the new set of diagnostic criteria introduced here.

Those minor criteria that are related to IgE dysregulation can be safely omitted. Immediate (type I) skin test reactivity and elevated serum IgE are related to the mandatory criterium. Some other minor features can be omitted because they are directly part of the atopy syndrome (recurrent conjunctivitis, food intolerance). The early onset of disease might be omitted, because it does not matter at what age atopic dermatitis presents for the first time, as long as there is an atopic diathesis. The tendency towards infections and the presence of impaired cell-mediated immunity might also be omitted because they are related to the immunological and inflammatory pathogenesis (18), also reflected by the presence of allergen-specific IgE. The influence of environmental and emotional factors is atypical. Of course, environmental factors play a role in a
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genetic disease that may become manifest at any age. In these diseases, environmental factors are instrumental in the genotype-phenotype switch. Allergens probably have that role. Emotional factors then play a role in many inflammatory and immune mediated reactions, and this is not specific for atopy.

Many of the original minor criteria thus remain, with some additional criteria described by Diepgen et al. We here propose to subdivide them over 4 subsets (Table 3), i.e. -a- related to (subclinical) eczema; -b- related to dry skin; -c- extra skin folds; -d- ophtalmological pathology. The genetic background of these abnormalities is not yet known. Similar to what has been said about the presence of allergen-specific IgE and the genetic predisposition to it, it is to be expected that the genes behind these minor criteria will be identified, before or after the identification of the biochemical abnormalities that might explain dry skin, extra skin folds, and the ophtalmological manifestations.

Table 3  The millenium additional criteria ('circumstantial evidence')

-a- related to (subclinical) eczema
- cheilitis
- nipple eczema
- pityriasis alba
- facial pallor / erythema
- orbital darkening
- cradle cap
- tendency towards non-specific hand or foot dermatitis

-b- related to dry skin
- xerosis
- ichthyosis
- palmar hyperlinearity
- keratosis pilaris
- perifollicular accentuation
- perlèche
- itch when sweating
- intolerance to wool and lipid solvents

-c- extra skin folds
- Dennie-Morgan infraorbital fold
- anterior neck folds
- auricular rhagades
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  - ophtalmological pathology
    - photophobia
    - anterior subcapsular cataracts
    - Hertoghe sign

The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis
Williams et al (19-22) have published a series of articles in which a new set of diagnostic criteria was proposed. These criteria were subsequently validated by them in a hospital (dermatology outpatient clinic) as well as in a schoolchildren setting. In order to qualify as a case of atopic dermatitis, they proposed that an individual must have an itchy skin condition in the past 12 months, plus three or more of the following: history of flexural involvement (skin creases), a personal history of asthma or hay fever (or in first degree relative when under 4 years old), a history of a generally dry skin in past year, onset of rash under the age of 2 years, or visible flexural dermatitis. Itchy skin thus was taken as a mandatory criterium, while we have made a choice for a more pathogenesis-related feature, the presence of allergen-specific IgE. Flexural involvement is one of the major criteria in all diagnostic systems. A history of asthma / hay fever is covered by our mandatory criterium of presence of allergen-specific IgE, which identifies the atopic syndrome. A history of xerosis is in the new additional criteria. Early onset has been omitted from the additional criteria as explained above. Presence of flexural dermatitis, finally, is covered by the principal criteria.

Thus, although the U.K. Working Party’s Diagnostic Criteria for Atopic Dermatitis are among the best validated, they do not rely on how atopy actually might be defined; the abnormality to produce allergen-specific IgE.

The Japanese Society of Dermatology Criteria for Atopic Dermatitis
Recently, a special committee of the Japanese Dermatological Association (JDA) has also addressed the issue of defining criteria for the diagnosis for atopic dermatitis (23). They stated that the widely used guidelines, such as those of Hanifin and Rajka, were found to be ‘inadequate’. The JDA defines atopic dermatitis as a pruritic, fluctuating, eczematous dermatitis, and ‘most individuals with atopic dermatitis have atopic diathesis’. Atopic diathesis is then defined as having a personal and/or family history of atopic diseases and the predisposition to overproduction of IgE antibodies.

The JDA thus recognizes the importance of IgE, but fails to be strict, leaving open the possibility to make a diagnosis of atopic dermatitis in individuals without the diathesis. Also, The JDA emphasizes the importance of general IgE levels, and does not recognize the presence of allergen-specific IgE as being central to this diathesis.
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The diagnostic features as such are well defined, patients needing to fulfill three clinical criteria; -1- pruritus; -2- typical morphology and distribution; -3- chronic or chronically relapsing course. As such these are identical to the principal criteria we also propose here. The minor features of Hanifin and Rajka do not get any recognition, with the exception of follicular papules that are a diagnostic aid, and ocular problems that are seen as significant complications together with Kaposi’s varicelliform eruption, molluscum contagiosum, and impetigo contagiosa.

Constitutional eczema and atopic dermatitis
We would prefer to use the term ‘constitutional eczema’ for those cases that do not fulfill our criteria but are close to it. The simple diagnosis of atopic dermatitis in children having involvement of the cheeks as well as having xerosis is not correct; these children might be diagnosed as having constitutional eczema, and when at a later point in time it becomes evident that they fulfill the mandatory criterium as well as the principal criteria, the diagnosis might be adjusted into atopic dermatitis. In the meantime, presence of additional criteria might allow the clinician to state that the patient has constitutional eczema, with some features making it reasonable to accept that it is indeed atopic dermatitis.

Conclusions
It is about time, at the beginning of a new millennium, that the knowledge developed in the past ten years on IgE dysregulation in atopy is incorporated in the diagnostic criteria. We suggest that the presence of allergen-specific IgE should be a mandatory criterium for the diagnosis of atopic dermatitis. We suggest that in addition, 2 of 3 principal criteria (pruritus, typical morphology and distribution, chronic or chronically relapsing) should be fulfilled for such a diagnosis. We also revise the minor features originally described by Hanifin and Rajka, divide them over 4 subcategories, and suggest that they should only be used as additional criteria. It is predicted that in the future, a better biological explanation for these newly categorized additional criteria will ensue. In the end, we expect that the diagnosis of atopic dermatitis will be by gene testing. For the time being, incorporation of the major immunological abnormality in atopy, i.e. production of allergen-specific IgE, should be mandatory for the diagnosis of atopic dermatitis.
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References


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