How to Define Atopic Dermatitis?

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KEYWORDS

• Atopic dermatitis • Eczema • Definition • Immunoglobuline E • Precision medicine

KEY POINTS

- Atopic dermatitis (AD) display a wide clinical phenotype, varying according to ethnic populations.
- The value of total immunoglobulin E as a single biomarker for atopy and/or the diagnosis of AD is questionable.
- We need a refinement of the diagnostic criteria for AD according to ethnic populations.
- Research should focus on the discovery and validation of biomarkers for a precision medicine approach improving the definition and clinical diagnosis of AD.
- Future biomarkers will allow a better stratification of AD for personalized prevention and therapeutic approaches.

INTRODUCTION

Atopic dermatitis (AD) is a paradigmatic disease that has always challenged the scientific community with regard to its origin and the wide spectrum of the clinical phenotype. The multiple denominations for this disease over the last century underline this lack of consensus with regard overall to the understanding of the origin of the disease.[1–4] The term AD was coined by Wise and Sulzberger in 1933[5] and has merely adopted over the time. In the last 2 decades or so, there have been a number of attempts to redefine the disease according to more modern insights based on epidemiologic studies, genetic findings as well as immunologic pathomechanisms underlying the disease.

Without going much into the discussion of whether or not the term AD is the most suitable one for this condition, one should notice that it has been always a tradition in medicine and particularly in dermatology that designations of the diseases usually are based on a composite name typically relying to a symptom on one hand and an adjective for the context of that symptom on the other. Typical examples for this kind of denomination are *mycosis fungoides, lichen planus, psoriasis vulgaris, lupus erythematodes* or in our particular case, *atopic dermatitis*. The scientific community nowadays acknowledges the complexity of the clinical phenotype and of the pathophysiologic background of AD. The phenotype may rather correspond with a common set of symptoms that the skin has found in his own language to express the various underlying mechanisms that we just start to understand. The term "skin disease" has recently been proposed for this particular situation.[6]

IS IT *ECZEMA* OR *DERMATITIS*?

Interestingly, although physicians mean the same syndromic situation called herein AD, depending on the countries the preferred name can be different and this phenomenon certainly has a significant impact for many different aspects of practical relevance.[1,4] For example, the term *eczema* is more commonly used in the UK and in countries of the Commonwealth, whereas *atopic eczema* and *atopic dermatitis* are rather used and mixed up in other countries. A particular situation is observed

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in China, where *eczema* and *atopic dermatitis* are considered as 2 different diseases (see below). Sticking to the original meaning of the word *eczema*, coming from the Greek word εκσειν (eksein), which means "boiling," this denomination, particularly without the adjective *atopic*, seems the less suitable because it strongly suggests a disease in an acute situation with vesicles as a major clinical sign. Based on that and with regard to the classical clinical symptoms of this condition, the word *eczema* would seem the less appropriate for this disease, in particular when the adjective *atopic* is not combined. Therefore, a new discussion has been started on an global level with the aim to harmonize at least the denomination of the condition because this is expected to have significant relevance for a more global approach in terms of research, education, prevention, and drug development.[4]

HOW TO DEFINE *ATOPY*?

Beside the wording *eczema* or *dermatitis*, the definition of *atopy* is probably much more challenging. When facing the particular situation of a special familiar hyperresponsiveness against allergens, Coca and Cooke[7] asked the philologist Edward Perry to find a suitable term. Finally, they agree to the artificial term atopy which is derived from the Greek word ατοποσ (atopos) and means "not in the right place, not in the precise place, unusual, strange." Since then, this nonmedical term survived overtime and has been accepted to describe this particular kind of syndrome including an involvement of different target organs, such as the skin, lung, nose, and/or eyes, while the immune system seems to mount a specific immunity with immunoglobulin E (IgE). However, although there is a consensus about what the scientific community overall means by *atopy*, there remains a never-ending discussion on how to best define this in a consensual definition. For instance, the probably best definition of atopy remains the following: "atopy is a personal and/or family tendency to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these individuals can develop typical symptoms of asthma, rhino-conjunctivitis and eczema/dermatitis."[8] The dilemma of this definition is that most of the scientists would stick to the proof on an IgE-mediated sensitization in a distinct individual to apply the term atopy. However, in the given definition, it seems obvious that the production of IgE is a consequence of this predisposition, and not the origin. This subtle distinction is of particular significance when it comes to consider the very early phase of AD, where a given individual starts to have typical clinical symptoms of the disease but the sensitization against environmental allergens cannot yet be detected because it is expected to appear during the course of the disease.[9] Therefore, the very early phase of AD in infancy (phase 1) is related to an atopic predisposition even if increased total IgE and/or specific IgE cannot yet be demonstrated, at least with the available panel of allergens and technologies.

WHAT ABOUT *INTRINSIC* VERSUS *EXTRINSIC* ATOPIC DERMATITIS?

Among the patients suffering from typical clinical symptoms compatible with the diagnosis of AD, there seems to be a subgroup in which the patients lack increased total IgE or specific IgE to common allergens. Interestingly, the same phenomenon as described for the disease itself with multiple different denominations, is reproduced for this particular subgroup for which different terms have been coined such as *intrinsic* AD,[10] *atopy form* dermatitis,[11,12] or *non–IgE-associated* dermatitis or *nonatopic eczema*.[8] As mentioned, normal IgE and/or the lack of detectable specific IgE can be encountered mainly in 2 situations: (i) in infancy or early childhood when the clinical dermatologic symptoms are present, but the sensitization process has not yet led to the generation of increased IgE synthesis.[13,14] Interestingly, many studies have highlighted the fact that the situation is more frequent in female individuals than in males.[15,16] Similarly, (ii) in the so-called late onset of the disease, this particular form affects mainly females with a rather mild form of the disease, emerging in the absence of increased total IgE or seemingly detectable specific IgE.[16,17] There is currently no convincing explanation for the fact that IgE sensitization occurs earlier and in a more pronounced way in males than in females.

However, the existence of a non–IgE-associated form of AD can be strongly questioned.[18] Indeed, the cutoff for the so called 'normal IgE' has been fixed at around 100 kU/L.[19] In contrast, the exploration of specific IgE is limited to a distinct more or less large panel of common allergens. Thus, we will always face the typical issue of the limitation of the value of IgE as a reliable biomarker to appreciate the atopic status of a patient and his very individual and personalized sensitization profile. In fact, most physicians have frequently faced the situation of patients with normal total IgE (<100 kU/L) but clear-cut oligosensitization to some relevant allergens such as house dust mite or pollens with significant proportion of specific IgE within