Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go?

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Atopic dermatitis (AD) is a paradigmatic chronic inflammatory skin disease characterized by a complex pathophysiology and a wide spectrum of the clinical phenotype. Despite this high degree of heterogeneity, AD is still considered a single disease and usually treated according to the "one-size-fits-all" approach. Thus more tailored prevention and therapeutic strategies are still lacking. As for other disciplines, such as oncology or rheumatology, we have to approach AD in a more differentiated way (ie, to dissect and stratify the complex clinical phenotype into more homogeneous subgroups based on the endophenotype [panel of biomarkers]) with the aim to refine the management of this condition. Because we are now entering the era of personalized medicine, a systems biology approach merging the numerous clinical phenotypes with robust (ie, relevant and validated) biomarkers will be needed to best exploit their potential significance for the future molecular taxonomy of AD. This approach will not only allow an optimized prevention and treatment with the available drugs but also hopefully help assign newly developed medicinal products to those patients who will have the best benefit/risk ratio. (J Allergy Clin Immunol 2017;139:S58-64.)

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Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder.[1] The disease represents a substantial socioeconomic burden,[2,3] partly because of the lack of an efficient therapeutic armamentarium able to control the disease in the long term.[4] Most of the physicians who take care of patients with AD are well aware of the high degree of heterogeneity of the clinical phenotype and the debated role of IgE-mediated sensitization or food allergy.[5,6] The latter is only one among many provocative factors claimed to be instrumental in inducing flares and/or supporting the chronic inflammation and itching sensation.

Our current understanding of the disease has dramatically evolved over the last years, mainly because of substantial progress in epidemiology and genetics, further supporting the concept of the atopic march[7] but also unraveling new aspects with regard to the natural history[8,9] and persistence of AD over a lifetime.[10,11] Many pioneering discoveries have unraveled the critical genetic predisposition underlying epidermal barrier dysfunction,[12,13] as well as the intimate immunologic mechanisms working as forces driving chronic inflammation,[14] and triggering the emergence of IgE-mediated sensitization[15] and contact sensitization.[16]

Despite the obvious complexity of the clinical phenotype, we are still treating AD according to the "one-size-fits-all" approach and are neglecting a more differentiated method based on stratification of AD.[17,18] Change will come through a better understanding of the different genetic and immunologic mechanisms underlying the wide spectrum of disease phenotypes. The roadmap toward a precision medicine approach in AD management will be mainly dictated by the discovery and validation of reliable biomarkers that will enable the physician to provide more tailored management, starting from prevention strategies and moving up to treatment of patients with more severe disease with targeted therapies.[19-21] A clear definition of different clinical phenotypes on the one hand and potential biomarkers providing the adequate respective endophenotypes are key elements for successful development of new therapeutic options[22] and implementation of precision medicine in patients with AD.

CLINICAL PHENOTYPES

Stratification based on the age-related clinical picture

The clinical picture of AD varies substantially depending on the age of the patient.[1] Typically, at least 4 different kinds of clinical features have been defined[23] as follows: infantile, childhood, adolescent/adult, and elderly. Although acute lesions predominate more in the infantile spectrum, chronic lesions,

Abbreviation used
AD: Atopic dermatitis

including strong lichenification, typically appear later and are sometimes combined into more nodular lesions corresponding to the prurigo phenotype. Except for the very initial stage of the disease during the first weeks of life, pruritus remains a typical hallmark in all stages.

Infantile AD (between 3 months and 2 years of age). The first lesions emerge around the second month of life and typically affect the cheeks with edematous papules and papulovesicles. They can form large plaques with oozing and crusting. The scalp also shows extensive scaling of the so-called cradle cap. Furthermore, the scalp, neck, and extensor parts of the extremities, as well as the trunk, can be involved, sparing the diaper area. Most importantly, the very initial stage of the disease might be very difficult to diagnose, whereas the more typical eczematous lesions on respective localizations can appear a few weeks later.

Childhood AD (age 2-12 years). At this stage, acute lesions still appear, but chronic lesions with some lichenification tend to be at the forefront. The predilection sites are the popliteal and antecubital fossa (flexural eczema), as well as the periorificial areas on the head. Quite often, the hands and wrists show rather nummular plaques with oozing and crusting corresponding to a nummular type of the disease. Dry skin (xerosis) becomes more dominant.

AD in adolescents and adults (age >12 up to 60 years). In this period of life, the lesions are more fixed to classical areas, such as the head, neck, and flexural areas. Moreover, in adults the disease can also affect the hands (chronic hand dermatitis). In female subjects the disease also often involves the periorbital areas. In patients with a long-standing natural history of the disease, AD is more likely to have an extensive and sometimes erythrodermic aspect.

AD in the elderly (age >60 years). This seems to be a rather underestimated clinical phenotype of AD (see "Natural history of AD"). This form is mostly characterized by extensive eczematous lesions up to erythrodermic aspects with a strong pruritic component. Sometimes the lesions spare the flexural areas. This particular phenotype certainly needs a more profound analysis to define clear-cut clinical criteria for its definitive diagnosis. In the elderly a number of differential diagnoses should be excluded that might mimic AD, such as allergic contact dermatitis and cutaneous T-cell lymphoma.

Stratification based on disease severity

As already mentioned, AD can cover a wide spectrum in terms of severity, ranging from very mild to very severe phenotypes. In addition to the classical diagnostic criteria, the definition of severity as mild, moderate, or severe is best obtained by using validated scoring systems, such as the SCORAD or Eczema Area and Severity Index scores. For the purposes of pivotal (phase 3) clinical trials, some regulatory agencies, such as the US Food and Drug Administration, request the so-called Investigator Global Assessment as a primary end point with a 5- or 6-point scale that has never been properly validated. An attempt to align these different scoring systems in a single chart is presented in Fig 1 (based on Leshem et al[24]). Such an alignment might be useful to compare the efficacy of primary or secondary end points from different studies, such as in a meta-analysis. There is still debate as to which scoring system is the easiest to use for physicians in daily practice, who face therapeutic decisions involving new active substances, such as biologics.

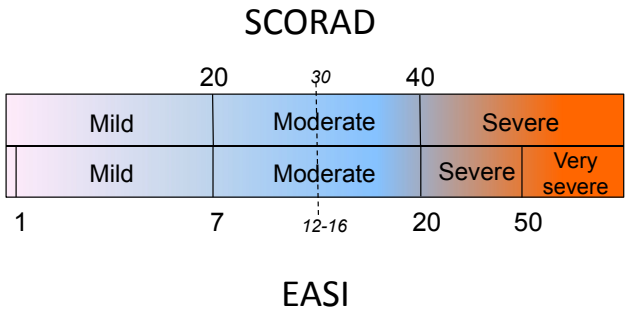

FIG 1. Clinical phenotype: stratification according to severity, as exemplified by SCORAD and Eczema Area and Severity Index *(EASI)* scores (based on Leshem et al[24]).

The so-called atopic stigmata, which represent clinical findings apart from eczematous lesions, might also represent particular variants of the mild forms of AD and are more helpful for a classification in relationship to the atopic diathesis.[25]

Stratification based on age of onset

Another way to stratify patients affected by AD is to classify them according to the natural history of the disease. This has many implications for our understanding of epidemiologic aspects and for our understanding of the dynamics of the disease, which can be imprinted by different kinds of immunologic mechanisms. Finally, being able to identify those patients with the highest risk of an ongoing chronic inflammation and a long-term disease history would provide significant progress in the targeted approach to prevention through early intervention. Although in the past AD was traditionally considered a disease primarily occurring in childhood and potentially resolving in a complete and definitive remission in more than 50% of patients up to age 10 years, more recent epidemiologic evidence supports the concept that, once acquired, AD can persist for the rest of a patient's life.

Follow-up studies of patients and retrospective analyses have identified at least 6 different types of onset of AD. In agreement with the notion that such phenotypes might represent distinct subentities is the observation that they are influenced by different environmental exposures effective at different ages. In support of this assumption, prenatal maternal contact with animals goes along with protection against AD manifesting during the first year of life,[26] whereas feeding habits during the first year of life are associated with AD with an onset after the first year of life.[27,28] These types of onset are summarized in Fig 2[9] and described below.

Very early onset (between 3 months and 2 years). Depending on epidemiologic studies, this type of onset represents 60% to 80% of all forms of AD onset. A substantial portion of patients can go into complete remission before age 2 years. Another portion, which is estimated roughly at 40%, continues to have the disease over a longer period of time and could represent the population with the highest risk for the atopic march.