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REVIEW

Changing perspectives in atopic dermatitis

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Abstract Atopic dermatitis (AD) is a multifaceted disease that involves a complex interplay between the skin and the immune system. The course of the disease depends strongly on the genetic background of the patient and on yet poorly-defined environmental factors. Changes in lifestyle could be behind the dramatic rise in the prevalence of AD across continents; including hygienic conditions, food, social habits, skin microbiome or exposure to a number of allergens. Although AD typically develops in childhood and disappears after a few years, in a relatively large number of patients it continues into adulthood. Adult AD can also appear *de novo* but it is often underdiagnosed and its treatment can be challenging. New, highly effective drugs are being developed to manage moderate and severe forms of the disease in adults. In this review, we highlight the most recent developments in diagnostic tools, current insights into the mechanistic basis of this disease, and therapeutic innovations.

Definition and diagnosis of AD

AD is a multifactorial skin disease

Atopic dermatitis (AD, atopic eczema) is a chronic, inflammatory, and intensely pruritic skin disease.[1,2] It is the most common cutaneous disease in children. AD is characterised

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by a hyperactive immune response to environmental factors and dry, itchy skin. Skin lesions can cause considerable psychological distress and a dramatic burden in the quality of life of patients and their families. AD is characterised for its fluctuations, its potential reversibility, and unpredictable progression in the life of the patient. Skin lesions can be triggered by stress, by contact allergens, and by scratching, among other factors. Onset of the disease in different periods of childhood has distinct outcomes later on and, although most cases resolve themselves in adolescence, a fraction of childhood patients develop the disease in adulthood.[3] Yet, AD can also develop *de novo* in adults or even at an advanced age.

Although the clinical manifestations of the disease can be surprisingly uniform, it is now known that AD presents a great degree of underlying heterogeneity. This heterogeneity stems from the variety and complexity of the mechanisms of pathogenicity of AD.[4] AD is a multifaceted disease resulting from the interaction network of the skin components (cellular and extracellular components contributing to the skin barrier), the immune system (innate and adaptive), and the skin microbiome.[1] The multiplicity of pathogenic factors has led to discussion of what components are more critical for triggering the disease, or which should be the target of therapies.

AD often occurs in families with atopic diseases, reflecting a strong genetic component in its pathogenesis. Still, the development and progression of AD can be greatly influenced by environmental factors. A large number of epidemiological studies have pointed towards diverse causes, many of which seem to have issues in common with the early development of the immune system and with triggers of chronic inflammation.[5]

AD can be a challenging disease to treat, especially in its more severe forms.[6] However, a number of novel therapies have emerged in recent years. Especially relevant are biologics targeting the immune system and in particular interleukins relevant to atopic diseases. These drugs hold especial promise for adult patients with moderate or severe forms the disease.[7,8]

Diagnosis of AD relies on clinical signs, allergy tests, and exclusion of other skin diseases

Diagnosis of AD is always made following clinical criteria and generally does not require complementary tests. The clinical presentation of AD depends on the age of the patients and the stage (acute or chronic) of the disease.[2,9] The criteria first defined by Hanifin and Rajka have been used for many years in the clinical diagnosis of AD,[10] and later also those of the UK working party.[11] Both systems are based mainly in the identification of atopic signs in the skin (especially skin folds) and time of appearance of the disease, among a number of other factors (Table 1). The diagnostic criteria listed can be found in most AD patients and should be sufficient to reach a definite diagnosis, especially in adults. Other skin conditions must be excluded when diagnosing AD, and often this requires complementary testing in the form of patch testing, prick tests or biopsy. Patch-testing for contact allergens is advisable in children and adults with moderate-to-severe AD, especially those with Eczema Area and Severity Index (EASI) scores greater than 10. It also should also be performed on adult patients refractory to treatments to exclude possible contact allergy sensitisation, or to those with a *de novo* skin eczema.[1,2,12,13] Patients with hand or foot dermatitis should always be patch-tested.[14] Prick tests should be aimed at detecting food allergies (mostly in children) or sensitisation to aeroallergens in adults with severe AD. Skin biopsy is unspecific as it shares findings with other eczemas, but can be considered as a confirmation of AD and to exclude other conditions such as dermatitis herpetiformis, early-stage cutaneous T-cell lymphoma, palmoplantar psoriasis, childhood scabies, or erythroderma, among others.

Currently there are no validated biomarkers that can readily help in the diagnosis of AD, although it is expected that some will emerge in upcoming years.[15] Although it has been estimated that about 80% of AD patients are sensitised through IgE to common allergens, routine IgE monitoring during diagnosis is not necessary.

Adult AD diagnosis must search for possible comorbidities such as asthma, rhinitis, conjunctivitis and food allergies.[16] However, AD in adults can present atypical morphology and localisation of skin lesions.[17] Some forms of presentation that are observed in adults include, for example, head-and-neck dermatitis, chronic hand eczema, and multiple areas or lichenification or prurigo lesions.[18] In Table 2 we show the procedures and tools currently available in the diagnosis of adult AD.[18] A Chinese group of dermatologists have recently advanced a minimal set of diagnostic criteria for AD in adolescents and adults. These criteria were based on questionnaires and dermatological examinations of 2662 patients.[19] They concluded that AD diagnosis must verify the presence of a symmetrical eczema (dermatitis) for more than six months plus one or more of the following:

- Personal and/or family history of atopic diseases
- Eosinophilia
- Elevated total serum IgE level and/or positive allergen-specific IgE.

AD severity can be evaluated with quantitative indexes

There are many indices developed to assess severity of AD described in the literature, mostly designed specifically to provide quantitative measurements in clinical trials. Routine clinical practice does not use severity scales to assess patients; however, collecting data regarding pruritus intensity, sleep disturbance or impact on daily activity, is encouraged.

The Scoring Atopic Dermatitis (SCORAD) cumulative index combines objective (extent and intensity of lesions) and subjective (daytime pruritus and sleep loss) criteria and it is widely used to quantify severity of the disease towards determining comparative efficacy of treatments and progression of the disease in clinical trials.[20] Thus, SCORAD scores of <25 reflect a mild, transient, form of the disease; a score of 25–50, moderate or recurrent AD; and >50 a severe, persistent form of AD. The Eczema Area and Severity

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