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GUIDELINES

Optimizing a clinical guidance for diagnosis of atopic dermatitis in adults: joint recommendations of the Italian Society of Dermatology and Venereology (SIDeMaST), Italian Association of Hospital Dermatologists (ADOI), and Italian Society of Allergological, Occupational and Environmental Dermatology (SIDAPA)

Cataldo PATRUNO [1] *, Paolo AMERIO [2], Andrea CHIRICOZZI [3], Antonio COSTANZO [4], Antonio CRISTAUDO [5], Francesco CUSANO [6], Caterina FOTI [7], Giampiero GIROLOMONI [8], Fabrizio GUARNERI [9], Luigi NALDI [10], Annamaria OFFIDANI [11], Paolo PIGATTO [12], Francesca PRIGNANO [13], Luca STINGENI [14], Piergiacomo CALZAVARA-PINTON [15]

[1]Section of Dermatology, Department of Health Sciences, Magna Graecia University, Catanzaro, Italy; [2]Department of Medicine and Aging Sciences, Clinic of Dermatology, G. D'Annunzio Chieti-Pescara University, Chieti, Italy; [3]Institute of Dermatology, A. Gemelli University Polyclinic, IRCCS and Foundation, Sacred Heart Catholic University, Rome, Italy; [4]Department of Dermatology, Humanitas University, Milan, Italy; [5]Department of Dermatology, San Gallicano Dermatological Institute, IRCCS, Rome, Italy; [6]Unit of Dermatology, G. Rummo Hospital, Benevento, Italy; [7]Section of Dermatology, Department of Biomedical Science and Human Oncology, University of Bari, Bari, Italy; [8]Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy; [9]Department of Clinical and Experimental Medicine-Dermatology, University of Messina, Messina, Italy; [10]Department of Dermatology, San Bortolo Hospital, Vicenza, Italy; [11]Unit of Dermatology, Department of Clinical and Molecular Sciences, Polytechnic Marche University, Ancona, Italy; [12]Unit of Dermatology, Department of Biomedical, Surgical and Dental Sciences, Galeazzi Orthopedic Institute IRCCS, University of Milan, Milan, Italy; [13]Unit of Dermatology, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy; [14]Section of Dermatology, Department of Medicine, University of Perugia, Perugia, Italy; [15]Department of Dermatology, ASST-Spedali Civili, University of Brescia, Brescia, Italy

*Corresponding author: Cataldo Patruno, Section of Dermatology, Department of Health Sciences, Magna Graecia University, Catanzaro, Italy.
E-mail: cataldopatruno@libero.it

ABSTRACT

Atopic dermatitis (AD) places significant burden not only on quality of life, but is also associated with considerable costs to healthcare systems. Diagnosis of AD may be challenging when it starts in adolescence or adulthood, and is further complicated as its manifestations are different from those generally seen in children. Accordingly, better definition of diagnostic criteria for adult onset AD is needed to avoid misdiagnosis and undertreatment in adult patients. To provide practical guidance for clinicians to reliably diagnose AD in adult patients, representatives from three Italian dermatology scientific societies (Italian Society of Dermatology and Venereology [SIDeMaST], Italian Association of Hospital Dermatologists [ADOI], Italian Society of Allergological, Occupational and Environmental Dermatology [SIDAPA]) carried out a joint consensus meeting to develop useful indications for improving diagnosis of moderate to severe AD in adult patients in routine clinical practice. The most representative criteria for morphological criteria, localization, clinical history, and differential diagnosis were identified by the experts. The most frequent clinical presentations are those on the flexural areas, hands, face/neck, and trunk, with itch and eczema as key manifestations. The diagnostic path defined herein can form a sort of "check list" for physicians to adopt when evaluating patients with suspected AD, which can help in refining a diagnosis and refer the patient for specialist dermatological care. It is hoped that the practical guidance developed by the consensus group will help to improve outcomes, lower overall costs of care, and ameliorate the patient's quality of life, even though validation in a large cohort of patients is still needed.

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KEY WORDS: Dermatitis, atopic; Guidelines as topic; Consensus.

Atopic dermatitis (AD) frequently appears in early childhood (15% to 30%) and usually resolves prior to puberty.[1] However, in up to half of patients it may persist into adulthood and become a lifelong condition.[2, 3] The term adult-onset AD was first coined in 2000 to describe patients in whom the disease presents *de novo* during adulthood.[4] Even if the exact prevalence of AD remains unclear, several studies have indicated that it has been increasing in recent decades, particularly in industrialized countries.[3, 5] Current estimates place the prevalence of AD at around 2-8% in adults, compared with 10-20% in children.[6-11] SCORing Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA), and Six Area Six Sign Atopic Dermatitis (SASSAD) are the most common instruments used to objectively measure disease severity, with SCORAD (mild, <15; moderate, 15-40; severe, >40) and EASI (mild, <7; moderate, 7-20; severe, 21-50; very severe ≥50) being the most widely validated.[12, 13] Most patients with AD have mild to moderate disease, while about 10-15% of moderate to severe cases require systemic treatment.[6]

Moderate to severe AD may place significant burden on both personal and social aspects, with substantial impairment in both health-related quality of life and work productivity.[14-16] Moderate to severe AD patients report itch in 85% of cases, 68% refer sleep disturbance caused by itch, and 22% describe psychological disturbances that include anxiety and depression.[15] Moreover, it has recently been linked to an increased risk of suicidal ideation.[17] Accordingly, the condition needs appropriate and efficacious treatment, which can only be achieved through early diagnosis.[1]

At present, diagnosis of AD is mostly based on the clinical experience of the dermatologist and is not generally problematic in children presenting with chronic relapsing-remitting eczema in characteristic body areas or in adults with similar lesions and a childhood history of AD.[8, 18-23] However, AD may be challenging to diagnose when it starts in adolescence or in adulthood, especially when its manifestations are different from those generally seen in children.[24]

Considering this scenario, better definition of diagnostic criteria for adult onset AD is needed in order to avoid both misdiagnosis and/or undertreatment in adult patients.[25-28] In fact, despite significant advances in our understanding of the etiology and pathogenic mechanisms underlying AD, at present no markers are available that can help clinicians in routinely reaching a definitive diagnosis of AD.[1]

To address these issues and provide practical guidance for clinicians to reliably diagnose AD in adult patients, representatives from three Italian dermatology scientific societies [Italian Society of Dermatology and Venereology (SIDeMaST), Italian Association of Hospital Dermatologists (ADOI), Italian Society of Allergological, Occupational and Environmental Dermatology (SIDAPA)] carried out a joint consensus meeting. The meeting was aimed at developing useful indications for improving diagnosis of moderate to severe AD in adult patients in daily clinical practice, also taking into consideration the most recent scientific evidence and expert clinical experience.

Specifically, there were three main tasks: 1) define the modalities of presentation (clinical phenotypes) and characteristics of AD in adults that differentiate it from the pediatric forms; 2) assess if current diagnostic criteria are adequate and precise in the identification of adult patients with AD who need treatment; 3) produce a consensus document to define a diagnostic path that will facilitate early and accurate diagnosis of adult AD.

Definition of guidelines

Materials and methods

The expert board was composed of 15 dermatologists, all selected on the basis of their expertise in managing adult AD, relevant scientific publications, and involvement in clinical trials on AD. A workshop type format was held on 12th June 2018 in Milan in order to discuss issues related to the diagnosis of adult AD in daily clinical practice, and to review the most recent scientific evidence and clinical experience. The limitations of current diagnostic criteria on AD were discussed and dialogue on the different pheno-

types of AD took place. The experts were then divided into two groups which had the task of concurrently identifying the most representative criteria for each of the following: morphological criteria, localization, clinical history, and differential diagnosis. The results from each group were then compared and unified in order to compile a definitive list that is useful for diagnosis in routine settings. The experts were then presented with a list of finalized recommendations, which was approved by all participants.

Results and discussion

Current diagnostic criteria and limitations

The main and currently employed diagnostic criteria and scores were reviewed. All were considered to have shortcomings that limit their sensitivity and specificity in daily practice, especially in the adult population. Indeed, AD in adults does not usually meet traditional diagnostic criteria for the disease as these were developed for children.[1]

Hanifin and Rajka Criteria

The 4 major Hanifin and Rajka criteria were not developed from a formal study, but rather from clinical experience; the 23 minor diagnostic criteria were developed using the pediatric population as a reference, have not been validated in adults, and are thus not sensitive or specific for the adult population. Moreover, these major and minor criteria are not suited for routine clinical practice, and some minor criteria are seen only rarely.[29]

Kang and Tian Criteria

These were considered to be more specific for an Asian population rather than Caucasians, and also give an excessive role to serum markers.[30]

UK Working Party's Criteria

The only objective criterion is the presence of itchy skin condition (or parental report of scratching or rubbing by child), and other criteria lack sensitivity. One of the 5 main criteria is the onset under the age of 2 years.[20]

Japanese Dermatological Association criteria for the diagnosis of AD

The use of diagnostic criteria by non-dermatologists is allowed, but this requires specific training as well as education on clinical dermatological evaluation. While suitable for community epidemiological studies, these criteria are difficult to apply in daily clinical practice.[31]

ISSAC criteria

These criteria use a 3-item anamnestic questionnaire based only on medical history, all of which must be present to reach diagnosis. Clinical data are not taken into account.[32]

Diepgen criteria

Although 13 features are considered in distinguishing AD patients, the definition of AD is related to relapses of flexural eczema (at least 3 relapses as the gold standard). A portion of patients, however, do not present with flexural eczema addition. There are also patients with flexural involvement that is due to pathologies other than AD, limiting its specificity.[33]

AAD Revision of UK Working Party's Criteria

These criteria recognize essential features (pruritus and acute, subacute, chronic eczema) and many patterns, including current or prior flexural lesions in any age group. Diagnostic criteria also comprise personal and/or family history of atopy and IgE reactivity, and are relatively complicated for routine use.[18]

Other attempts have been made at defining specific diagnostic criteria for AD in adults, noting that clinical presentations are often very heterogeneous, and that the same diagnostic criteria may not be applicable to all populations.[8, 34]

Additional considerations

A recent Italian consensus document using Delphi methodology was produced, although the statements generated do not contain specific criteria for diagnosis of AD, but focus rather on its management[35] SCORAD, EASI, IGA, and SASSAD scales were all overviewed and their utility acknowledged; it was reported that only EASI shows high internal consistency and emerged as the preferred tool in the Italian clinical practice as a basis to define AD severity. Moderate-to-severe AD is defined as an AD with EASI score ≥16 or with EASI score <16 when the disease is located on the face, hand, or genitals, and/or itch Numerical Rating Scale (NRS) >7 (on a scale 0 to 10), and/or sleep disturbance NRS>7, and/or Dermatology Life Quality Index >10 (on a scale 0 to 30). It was also highlighted that current diagnostic criteria were mostly derived from pediatric populations, which have clinical aspects that are different in adults, and that those specific for adults are not validated. Moreover, a key conclusion that emerges from most guidelines is that the clinicians' experience is fundamental.[36] In addition, the diagnostic criteria current-

ly available for adult AD are difficult to apply in practice as they lack adequate sensitivity and/or specificity. Some systems are not practical for routine use and/or may not accurately reflect or evaluate the clinical presentation, especially in patients with adult onset AD. It was further noted that AD may have early or late onset. Many cases of AD with childhood onset may also have manifestations in adulthood. A recent meta-analysis reported that among adults with AD, the proportion of adult onset AD is 26.1%.[37]

While clinical history is important, in the opinion of the experts' clinical history alone is neither specific nor sufficient for diagnosis as in the adult forms there may be no significant history. All available diagnostic criteria are based on epidemiological analyses and thus are more relevant at providing a system for the diagnosis of AD on large populations worldwide, and not for clinical evaluation of the individual patient in a clinical setting. Thus, it was deemed that a new system is needed that can improve the identification and classification of adult patients with AD with a practical focus, based not only on clinical history. Such a system would start with direct assessment of lesions and manifestations, using expert consensus on specific and sensitive clinical features for differential diagnosis of adult AD *vs*. other forms of dermatitis.

Clinical phenotypes of AD

Recognition of clinical phenotypes of AD is mandatory, considering that AD may have early or late onset and many cases of AD with childhood onset may also have manifestations in adulthood. Moreover, a recent meta-analysis reported that among adults with AD, the proportion of adult onset AD is 26.1%.[37]

Eczema should be considered as an essential criterion for diagnosis of AD. While eczema is straightforwardly recognized by expert dermatologists, it may be more difficult to identify among non-dermatologist physicians. In addition, eczema is generally characterized by notable phenotypic variation that renders it complex to identify.

Various clinical characteristics and modes of presentation were also taken into consideration. Acute and chronic eczema can clearly overlap given the recurrent nature of the condition.[38] Several morphological clinical phenotypes have been identified.[38] Localized variants of eczema comprise hand eczema, plantar dermatitis, cheilitis, nipple dermatitis, and periorificial dermatitis.[38] In adults, AD may be clinically similar to that seen in later childhood, with lichenification, especially of the antecubital flexures, eyelids, perioral region, and popliteal flexures.[38] Occasionally, adult AD has atypical morphologic features such as nummular dermatitis-like lesions, follicular, prurigo nodularis-like lesions, and seborrheic-like dermatitis.[38] Commonly involved regions include the forehead, cheeks, and anterolateral region of neck.[38] Other authors have noted that adult AD may frequently diverge from a classic pattern of flexural dermatitis and head-and-neck dermatitis, since chronic eczema of the hands, multiple areas of lichenification, or prurigo lesions are often considered typical of this form of AD.[1]

Facial pallor has frequently been suggested by many clinicians to be diagnostic, together with typical palpebral signs, namely the Dennie-Morgan sign (one fold or several folds beneath the lower eyelid), dark circles (orbital darkening), and Hertoghe sign (thinning or alopecia of the outer third of the eyebrows) For correct diagnosis of AD in adults, minimal AD must also be considered, such as mild eczema localized only to the eyelids or around the lips or a single variant of the disease such as pityriasis alba or stigmata of the atopic facies.

The experts emphasized that while some specific clinical signs are obviously relevant, it is also important to evaluate how the different manifestations present considering the overall situation of the individual patient.

Diagnostic standards

In considering diagnostic standards for AD in adults, the overall objective was to identify a set of sensitive and simple features that can be easily adopted in non-specialist settings to improve initial screening for AD in adults so that patients can be referred to specialist centers for confirmation of diagnosis. Using such a strategy, it was hypothesized that the management can be optimized and patients may then receive better care.

The criteria involved four major areas that are presented below: morphological features, localization, clinical history, and differential diagnosis. As mentioned, the experts were divided into two groups and asked to identify 3 to 4 of the most relevant features for each pillar. The outputs were then compared, unified, and approved in a plenary session.

Morphological features

The morphological features identified are shown in Table I. Both acute and chronic eczema were considered to be the key aspect for diagnosis of AD, although eczema is often not recognized and is underestimated by many physicians in ambulatory settings. Moreover, pruritus is a typical component of AD.

TABLE I.—*Diagnostic features for atopic dermatitis in adults.*

Criteria	
Morphological	• Eczema (acute and chronic) • Skin xerosis • Lichenification • Excoriated papules and nodules (prurigo) • Facial signs*
Localization	• Hands** • Face/neck** • Flexural areas** • Torso • Nipples • Symmetry/diffusion
Clinical history	• Positive family history (first degree) • History of or previous episodes of any type of AD • History of rhinosinusitis, allergic rhinitis, or asthma
Main differential diagnoses	• Contact dermatitis [allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD)] • Cutaneous T lymphoma • Scabies • Adverse drug reactions • Psoriasis • Tinea • Pityriasis rosea, seborrheic dermatitis

*Facies with typical palpebral signs, perioral eczema, plica under orbital/dark circles Dennie-Morgan line, omnibus sign, pale skin.
**Characteristic localizations.

Localization

The body areas identified as most affected are those listed in Table I. All of the sites listed were considered to be important: flexural areas, hands, face/neck, and trunk/nipples, with the latter being of particular relevance in nummular eczema-like lesions. In the adult, AD may also be located in other body areas (*e.g.* genitals, ears, and other locations).

Clinical history

Personal history of AD and mucosal atopy are relevant, but in the assessment of clinical history it is necessary to identify family history for any type of AD, as well as mucosal atopy (rhinosinusitis, rhinitis, conjunctivitis, or asthma). Family history of AD should be limited to first degree relatives.

Differential diagnosis

The main differential diagnoses include allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD), cutaneous T-cell lymphoma, scabies, and adverse drug reactions. Seborrheic dermatitis and psoriasis (in particular inverse psoriasis), as well as dermatophytosis, should also be taken into consideration.

Biological markers

High levels of immunoglobulins E (IgE) and/or circulating eosinophils are often found in patients with AD, but their presence in the absence of cutaneous features of the disease cannot help in making a diagnosis of AD; furthermore, they can be also found in healthy, non-atopic individuals.[18] The search for a specific IgE can be sometimes helpful when sensitization to various allergens is suspected, because in selected cases preventing exposure to the allergens and specific immunotherapy may improve or prevent AD relapses.[39] Patch testing should be performed in a patient with atopic eczema, especially of the hands, when AD does not respond or worsens with topical treatment.[40] In fact, the protracted use of skincare products or topical drugs, associated with the impaired skin barrier of atopic children, enhances the risk of sensitization to the ingredients of these products not only in children,[41] but also in adult patients with long-lasting disease.[38] This is the case for some contact allergens, such as fragrances, some preservatives, and topical drugs (*i.e.* topical corticosteroids and antibiotics). After patch testing, the relevance of patch test positivity should be highlighted, clarifying which positive reactions to patch tests are not clinically meaningful.[42] In order not to cause confusion for the patient, it is extremely important to assess the clinical relevance of positivity for the test, highlighting the positive reactions to the patch test that are not clinically relevant.[40]

Limitations of the study

The practical guidance discussed herein may have some limitations. Firstly, it was conceived with the idea that a first-tier physician would use the criteria to refer patients to specialist care, and thus may not cover all possible diagnostic issues, and may not be applicable in all settings. Second, the diagnostic features identified by this consensus group are only the first step that can lead to the development of more formal diagnostic criteria; for this purpose, validation in a large cohort of patients presenting to ambulatory clinics with follow-up data is required.

Conclusions

The diagnosis of AD is largely clinical, and while it is relatively easy in children, it is often more difficult in adults unless the individual has had the condition since a younger age. Moreover, in adults, both clinical features and morphological characteristics of AD are often different from

those seen in children.[43] The most frequent clinical presentations are those on the flexural areas, hands, face/neck, and trunk, with itch and eczema as key manifestations, even if other variants should not be considered as uncommon. Diagnosis of AD in adults has remained a clinical challenge since to date there are no specific criteria for the adult population.

The diagnostic path identified and defined herein forms a sort of 'check list' for physicians to adopt when evaluating patients with suspected AD, which can help them in refining a diagnosis and refer the patient for dermatology specialist care. This is an important aspect, since early diagnosis is likely to improve outcomes, lower overall costs of care, and ameliorate the patient's quality of life. Early diagnosis and treatment may further help decrease the overall morbidity of the disease and prevent its progression to other atopic diseases.[44] Moreover, the importance of early diagnosis should be seen in light of the increasing number of effective treatments that can be offered to patients, such as dupilumab,[45] which has been shown to improve not only the signs and symptoms of AD, including pruritus, but also symptoms related to anxiety, depression, and quality of life.[46, 47] Other novel therapies are also in the pipeline, which include a topical PDE4 inhibitor and oral JAK inhibitors, with promising results.[48] Indeed, targeted therapy will likely complement traditional treatments and increase the opportunity for personalized treatment. However, it should be stressed that patients cannot benefit from any treatment unless they are properly diagnosed.

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