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Atopic dermatitis in adults: clinical and epidemiological considerations☆

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ABSTRACT

Objective: Atopic dermatitis (AD) is a chronic inflammatory disease causing intense pruritus, and with typical clinical features. There are few epidemiological studies concerning AD in adults, as well as little information about its prognostic. The aim of this study was to evaluate the clinical and epidemiological course of adults with AD.

Methods: 80 patients aged above 18 years (mean age = 29 years) were selected (30 males and 50 females) and interviewed about hospitalization, systemic corticoid usage, age of AD onset, and personal and/or familial history of atopy. Disease severity was evaluated through the Scoring Atopic Dermatitis (SCORAD) tool. Laboratory examination included IgE serum levels and eosinophil blood count.

Results: 71 out of 80 patients referred association with respiratory symptoms (18 had asthma, 17 had rhinitis, and 36 had both conditions); nine out of 80 patients denied any respiratory disease. AD patients were divided in mild (n = 25), moderate (n = 30), and severe (n = 25); 56% had one or more hospitalizations due to AD. A positive association was found between IgE serum levels, eosinophil blood count, and disease severity.

Conclusion: Adult AD represents a clinical challenge that needs to be better characterized, since it can be misdiagnosed and interferes with the patient's social and personal life. The association of skin and respiratory atopic disease is frequent, and laboratory parameters such as circulating IgE levels and eosinophil blood count may be helpful to assess disease severity.

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Dermatite atópica em adultos: considerações clínicas e epidemiológicas

RESUMO

Objetivo: Dermatite atópica (DA) é uma doença inflamatória crônica com prurido intenso e características clínicas típicas. Há poucos estudos epidemiológicos a respeito da DA em adultos, bem como pouca informação disponível sobre o seu prognóstico. O objetivo do

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☆ Study conducted at the Medical School of the Universidade de São Paulo, São Paulo, SP, Brazil.

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presente estudo é avaliar as características clínicas e o curso epidemiológico dos adultos com DA.

Métodos: Foram selecionados 80 pacientes com idade acima de 18 anos (média de idade = 29 anos, 30 homens e 50 mulheres), que foram entrevistados sobre: internações, uso de corticóide sistêmico, idade de início da DA, história pessoal e/ou familiar de atopia. A gravidade da doença foi avaliada de acordo com o SCORing Atopic Dermatitis (SCORAD). A avaliação laboratorial incluiu dosagem sérica de IgE e contagem sanguínea de eosinófilos.

Resultados: 71 dos 80 pacientes referiram associação com sintomas respiratórios (18: asma, 17: rinite alérgica e 36: ambas as condições); nove dos 80 indivíduos negaram qualquer sintoma respiratório. Os pacientes com DA foram divididos em DA leve (n = 25), moderada (n = 30) e grave (n = 25); destes, 56% tiveram uma ou mais internações por conta da doença. Verificou-se uma associação entre níveis séricos de IgE, contagem sanguínea de eosinófilos e gravidade da doença.

Conclusão: A DA do adulto representa um desafio clínico que necessita ser melhor caracterizado, uma vez que pode ser erroneamente diagnosticada, e interfere diretamente na vida social e pessoal dos pacientes. A associação entre manifestação respiratória e cutânea é frequente, e parâmetros laboratoriais como níveis de IgE circulante e contagem sanguínea de eosinófilos podem ser úteis para acompanhar a gravidade e evolução da doença.

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Introduction

Atopic dermatitis (AD) is a pruritic, chronic, and inflammatory disease, with typical clinical features. AD is one of the most common skin diseases, with a prevalence of 10% to 20% in children and 1% to 3% in adults.^{1,2} Diagnosis is based on clinical findings,³ and despite the existence of a wide number of disease outcome measures, three scores (EASI, Scoring Atopic Dermatitis [SCORAD], and POEM) have been adopted by the majority of the studies.⁴⁻⁸

In 30% to 50% of the AD patients, the disease markedly improves during elementary school-age or adolescence. Among those, AD patients that present the disease until adulthood, 50% to 60% persist with a chronic, recurrent course.⁹

The pathogenesis of AD remains complex. Gene-environment interactions in genetically predisposed individuals play a central role.¹⁰ Moreover, there is a variability of systemic and skin immune abnormalities in AD, such as increased serum IgE and allergen sensitization, abnormalities in epidermal barrier (gene mutations encoding proteins such as filaggrin), the Th1/Th2 paradigm, and microbe skin colonization.^{1,10,11}

The skin barrier function has been considered a protective factor against the development of AD, since inherited abnormalities in critical epidermal proteins have been identified in recent studies of AD patients. One of these proteins is filaggrin (FLG), a granular cell layer key protein that is processed from profilaggrin and facilitates terminal differentiation of the epidermis.¹² FLG is responsible for the aggregation of keratin filaments, which collapse the granular cells into nuclear squames to form the cornified cell envelope of the stratum corneum (SC) and the skin barrier, protecting the organism against environmental agents and preventing epidermal water loss.¹³⁻¹⁵ Skin barrier defects caused by FLG mutations allows the penetration of allergens through the epidermis and their interaction with antigen-presenting cells, leading to the development of atopic disorders, including asthma and rhinitis.¹⁶ Recent studies demonstrated that FLG mutations

are strongly associated with increased atopic eczema risk, and probably account for approximately 10% of cases in Europe.¹⁷

AD has been classified into two groups: extrinsic form (classic IgE-mediated allergic) and intrinsic form (non-allergic).¹⁸ FLG mutations have also been linked to extrinsic AD in recent studies, indicating that high IgE serum levels may correlate with disease severity and skin barrier defects.¹⁹

Recent literature suggests that circulating eosinophil counts could be used as a diagnostic tool to differentiate extrinsic from intrinsic AD. Eosinophil blood count correlates with disease severity, similar to circulating IgE levels. Eosinophilia and eosinophil skin infiltration found in AD patients link AD to cytokines recruitment, and chemokines and eosinophil activation.²⁰

In the skin, AD presents as a model of Th1/Th2 response with a biphasic pattern: in acute lesions, a great number of interleukin (IL)-4, IL-5, and IL-13 (Th2-type cytokines) are found, whereas in chronic lesions there are high levels of IL-5, IL-12, and IFN- γ (Th1 cells).¹ Interleukin-4 and IL-13 are implicated in the initial phase of tissue inflammation, and may mediate an isotype switching to IgE synthesis, and up-regulation expression of adhesion molecules on endothelial cells. IL-5 increases the survival of eosinophils, and eosinophilia with an increase of the eosinophilic cationic protein (ECP) correlates to disease severity.²¹ Recently, regulatory T-cells with immunosuppressant activity in AD, such as IL-17, secreting Th17 cells and Th22 (IL-22 secreting cells) have been investigated in several studies.^{10,22,23}

Staphylococcus aureus is present in 80% to 100% of AD skin, and is responsible for the disease relapsing course. *S. aureus* exacerbates AD by secreting toxins and superantigens which stimulate T cells and macrophages. Most AD patients produce specific IgE antibodies against staphylococcal enterotoxins that correlate with disease severity. Superantigens can also induce corticosteroid resistance, suggesting that several mechanisms are implied in triggering AD flares.^{1,10,24,25}

Little information is available regarding the prognosis of AD adult patients. A monthly follow-up study was conducted in



Fig. 1 – Clinical features of AD in adults. A. Facial involvement in atopic dermatitis-extensive lichenification of the front, periorbital areas, and malar regions, sparing the central seborrheic areas. B. Severe AD, with erythema, xerosis, and massive lichenification of the inferior limbs.

adults with AD for ten years, and showed that high levels of circulating IgE and eosinophil counts as early as the first visit were indicative of persistent AD.²⁶

This study aimed to evaluate adults diagnosed with AD, with emphasis on their clinical and epidemiological course.

Methods

The patients were selected from the Atopic Dermatitis Out-patient Clinic of the Department of Dermatology from the Medical School of the Universidade de São Paulo, Brazil. Between December, 2010 and April, 2011, 329 patients diagnosed with AD (according to Hanifin & Rajka's criteria)³ were evaluated; 115 were above the age of 18, and 80 of those agreed to participate in the study after signing the informed consent (approved by the Ethics Committee of the Medical School of the Universidade de São Paulo). They were interviewed and classified according to the SCORAD (5) (Fig. 1A and B).

All participants answered a questionnaire that included data about their AD history, age of disease onset, use of systemic corticosteroids or other immunosuppressant drugs (e.g. methotrexate or cyclosporine), hospitalization, and personal and/or familial history of atopy. All included patients were using first-line therapy for disease control (e.g. emollients and topical corticosteroids).²⁷ IgE serum levels were detected by nephelometric method (N Latex IgE Mono, Dade Behring – Marburg, Germany). Levels up to 100 IU/mL were considered normal. Blood tests were performed to evaluate circulating eosinophil counts (normal levels: 0.0% to 5.0%).

Statistical analysis

Mann-Whitney and Kruskal-Wallis non-parametric tests were used to compare two or three sets of data, respectively. Correlation between data was established using

Spearman's- non-parametric correlation test. Difference between groups was considered statistically significant when $p\text{-value} \leq 0.05$.

Results

Demographic data included: 80 adults with AD, aged 18 or older (ranging from 18 to 79 years, mean age 29), and gender distribution: 30 males and 50 females. 71 of 80 AD patients reported association with respiratory diseases (18 had asthma, 17 had rhinitis, and 36 had both conditions); nine denied any respiratory illness. SCORAD ranged between 0 and 100, and AD patients were classified as mild ($n=25$), moderate ($n=30$), and severe ($n=25$). 56% of the AD patients (44/80) had one or more hospitalizations during their life, showing the impact of the illness on their quality of life. Systemic corticosteroid usage, (but not adjuvant oral immunosuppressant) such as cyclosporine or methotrexate,²⁷ was reported by 57 AD patients, and was followed by flares after tapering initial doses (Table 1).

Mean circulating IgE levels in AD patients was 18,340 UI/mL (Fig. 2A). There was an association of IgE levels and disease severity (Fig. 2B). However, no relationship was found between serum IgE levels and respiratory disease (Data not shown). A positive correlation between eosinophil blood count and disease severity SCORAD (Fig. 2C) was detected.

Discussion

AD is one of the most frequent dermatoses in the pediatric population; approximately 40% of the patients persist with the disease in adulthood. Although rare, the onset of AD may occur in adults, usually after the third decade of life.²⁸ Adult AD is complex, and the disease affects personal and familial dynamics.^{29,30}

Table 1 – Demographic data, hospitalization, systemic corticoids usage, and disease severity in adults with atopic dermatitis (AD).

Patients	n = 80
Gender (male/female)	30/50
Age (years)	18-79
Mean age	29
Age of disease onset (years)/n	0-2/19 3-11/21 Above 12/40
SCORAD (0-100)	Mild - n = 25 Moderate - n = 30 Severe - n = 25
AD and asthma	n = 18
AD and rhinitis	n = 17
AD, asthma, and rhinitis	n = 36
Hospitalization	n = 44
Systemic corticoids usage	n = 57

The present study aimed to characterize the profile of AD in adults, which corresponds to one-third of the total AD patients registered at this specialized unit. The association with respiratory disease was present in 71/80 AD patients, and exclusive dermatological involvement occurred in 9/80 patients. In a national study from Taiwan, the concomitance of respiratory involvement with AD was approximately 50%.²⁸

Regarding demographic features, gender differences in AD vary in several studies.^{31,32} Gender, however, does not appear to be a relevant marker of AD in adults. In the present study,

a prevalence of females was observed (63% females and 37% males).

Hospitalization was a relevant item in the applied questionnaire. It was present in 56% of the interviewed patients, and reflected how AD impacts the patient's and family's quality of life. Interestingly, it differs from other centers, where hospitalization reaches less than 0.2%, and occurs due to complications from infectious diseases associated to AD.³¹ Another topic was the use of systemic steroids, not routinely recommended for AD due to their side effects; 72% percent of the present AD patients related use of systemic corticoids, usually self-medicated.³¹

Circulating IgE levels are usually elevated in the majority of AD patients, and are reported to be associated with allergen-specific IgE status.¹⁸ In the present subjects, only one of 80 patients showed normal serum levels (up to 100 UI/mL), in contrast to the majority of patients, who presented an average IgE serum level of 18,340 UI/mL. The present data are in agreement with the literature, which shows that the majority of AD patients have high IgE levels, in a clear predominance of the extrinsic pattern. Moreover, IgE serum levels correlate with disease severity, suggesting that physicians should dedicate great care to patients with elevated IgE serum levels, reinforcing education and compliance.²⁶

Unfortunately, so far there are no specific laboratory markers to evaluate AD severity, but high IgE serum levels and eosinophil blood count are frequently found in AD patients. Some studies consider that a future perspective in

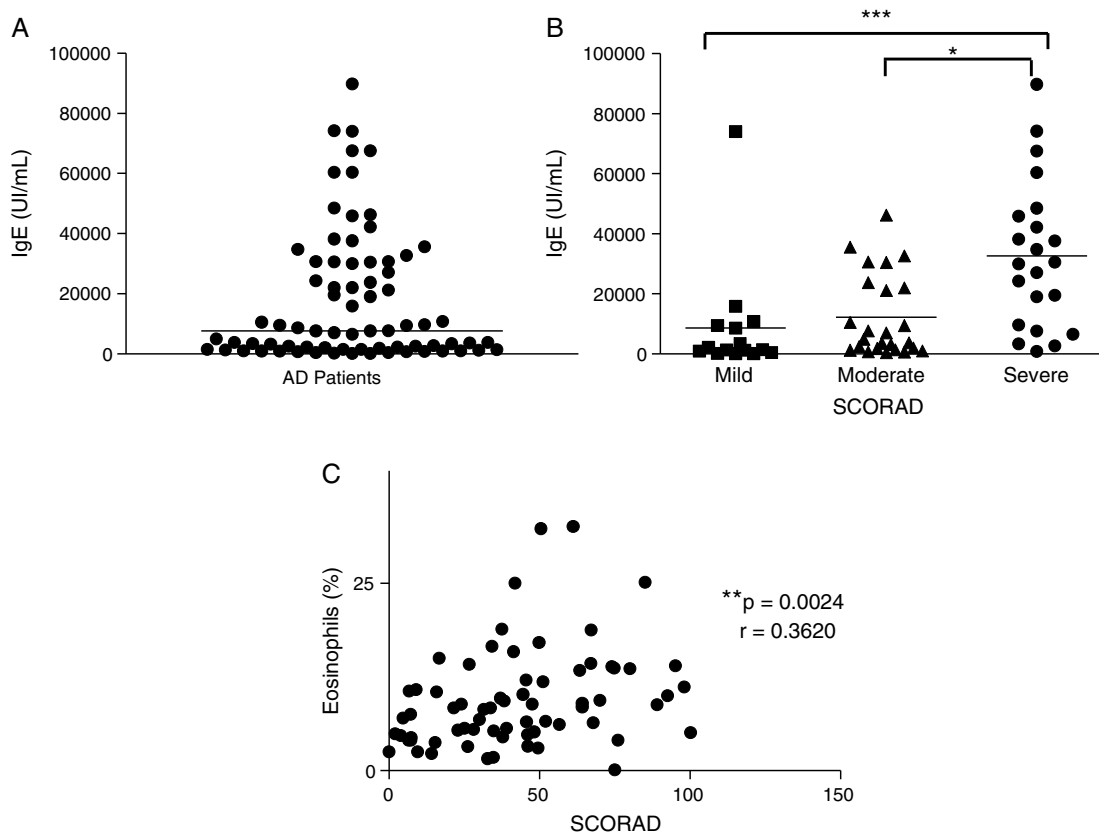


Fig. 2 – Evaluation of IgE, eosinophils and disease severity. A. Total IgE serum levels in AD patients. B. IgE serum levels of AD patients distributed according to disease severity. Line represents mean of IgE secretion expressed in UI/mL. C. Positive correlation between eosinophils blood count and disease severity. * $p \leq 0.05$; ** $p \leq 0.005$; * $p \leq 0.0005$.**

the treatment of AD may be based on serological markers such as IL-4.²¹ Some studies suggest that eosinophil blood count may be used as an indicator to distinguish intrinsic from extrinsic forms of AD, and others show that eosinophil blood count correlates with both disease severity and IgE serum levels.²⁴ All AD patients included in the present study showed high eosinophil blood counts (mean value = 9.45%; normal levels = 0% to 5%). A positive correlation between eosinophils and disease severity was found ($p = 0.0024$; $r = 0.3620$), but no correlation between IgE serum levels and eosinophil blood count was detected.

In conclusion, the present study presented an elevated number of adults with AD in this clinic, indicating that a careful follow-up, together with an education strategy are needed, since this is a chronic and high-cost disease with expressive social and economic implications. IgE serum levels and/or eosinophil blood counts present a positive correlation with disease severity, and are relevant parameters for managing this difficult and chronic disease, contributing to new strategies of treatment.

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This work was approved by the Ethics Committee of the Faculdade de Medicina da Universidade de São Paulo on May 28, 2010.

Conflicts of interest

The authors declare no conflicts of interest.

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