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Allergic, Cardiovascular and Psychiatric Comorbidities in Adult AD Patients - A Brazilian Study

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Abstract

Introduction: atopic dermatitis (AD) can be associated with allergic diseases such as rhinitis, asthma and food allergies. Recently, it has been be considered a systemic disease, with neuropsychiatric, cardiovascular (dyslipidemia, obesity and hypertension) and neoplasms as comorbidities. Objectives: to analyse the prevalence of AD comorbidities in adult patients at a dermatological center. Methods: retrospective, cross-sectional, comparative study using medical records of adult dermatological patients, between 2018 and 2019. The following comorbidities were investigated: rhinitis, asthma, food allergy, hypertension, obesity, depression and anxiety. Results: allergic comorbidities were shown to be statistically higher in the atopic dermatitis group, for all of the diseases studied (p <0.05). Regarding cardiovascular and psychiatric comorbidities, there was no statistically significant difference between atopic and non-atopic groups. Study Limitations: unicentric study with small number of patients. Conclusions: allergies were more prevalent in the AD population compared to the control group, which should be considered while investigating dermatitis in adults, even though there is no history of juvenile atopy. There was no higher prevalence of the comorbidities investigated in the atopic group in comparison to the control group. However, the prevalence of psychiatric comorbidities was high, in consonance with the current literature, reinforcing the importance of a detailed investigation in adult patients with AD.

1. Introduction

Atopic dermatitis (AD) is a chronic and recurrent allergic skin disease, which usually appears in childhood. It has been progressively considered as a public health problem, due to its increasing incidence, especially in countries with a higher socioeconomic level, in addition to its various implications for the individual's health [1].

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Its etiopathogenesis involves a dysfunction of the skin barrier, which has been considered the main phenomenon for the development of the disease, associated with mutations or inadequate expressions of the gene encoding of philagrin (a fundamental protein for epidermal integrity) added to an unregulated lipid metabolism, with decreased ceramides [2,3].

The barrier damage leads to the appearance of lesions with an eczematous pattern, which often lead to secondary infections, related to the proliferation of *Staphyloccocus aureus*, resulting from an alteration of the cutaneous microbiome [4].

Atopic dermatitis can be associated with other *IgE*-mediated allergic diseases, such as rhinitis and asthma, in addition to food allergies; and the chronology of these manifestations is recognized as atopic march, with frequent onset in early childhood [2,5]. However, dermatitis can develop late, in adulthood, in a lower percentage of cases [6]. Sensitization to foods and air allergens may occur due to their penetration into the injured skin itself, also leading to rhinitis, asthma and intolerance to certain foods [7].

Recently, the nature of AD has been considered as disease systemic, associated with non-allergic comorbidities, such as: neuropsychiatric, cardiovascular and neoplastic disorders [8,9].

Chronic stress added to pruritus and allergic conditions, although there are still few studies about it, triggers mental alterations, especially anxiety and depression, which can worsen the itching sensation [10,11].

AD is also related to other risk factors, such as dyslipidemia, obesity, hypertriglyceridemia and hypertension. Starting from the premise that the skin is a target organ of functions regulated by insulin and the pathogenesis of inflammatory diseases, it is postulated that this group of diseases should be seen as a sign of metabolic syndrome; some authors even suggest that screening for metabolic diseases should be considered in all patients with atopic dermatitis [12,13].

Adults with AD are significantly more likely to have a history of hypertension, adult-onset diabetes and hypercholesterolemia, even after body mass index control and / or allergic comorbidities; Cardiovascular risk increases even more when fatigue and sleep disorders are present, as well as the adoption of harmful health behaviors, such as smoking, alcoholism and physical inactivity [14].

From an epidemiological point of view, however, there is still limited information regarding the prevalence of comorbidities in the adult population. A cross-sectional study with a population of almost 50,000 individuals from 8 different countries in the Northern Hemisphere showed that the prevalence of AD in adults ranged from 2.1% to 8.1%, aligned with the data provided by the World Allergy Organization, being more common in women than men and less frequent in older people. However, the study also observed a considerable variation between the proportion of more severe forms and allergic comorbidities and the regions studied, suggesting regional variability [15].

In Brazil, there is still no data published on this topic.

The present study aims to evaluate the prevalence of comorbidities in adult patients with atopic dermatitis, collected in a private dermatological center (MEDCIN Dermatologia, Osasco, Brazil), comparing the results with the findings with the literature.

2. Objectives

To analyse the prevalence of atopic dermatitis comorbidities in adult patients from a private dermatological center.

3. Methods

Retrospective, cross-sectional, comparative study, conducted from a survey of electronic medical records filed in a software for this purpose (RACIMED, Brazil) of all patients in a private outpatient dermatology center (MEDCIN Dermatologia, Osasco, Brazil) between 01/01/2018 to 01/01/2019, with clinical diagnosis of atopic dermatitis, over 12 years of age (adult phase). In parallel, patients with other non-atopic pathologies were randomly surveyed to form a control group.

To form group 1 (group of atopic dermatitis), 127 medical records were collected containing the diagnosis of atopic dermatitis in patients older than 12 years old for data analysis.

To compose group 2, (control group - without atopic dermatitis), 180 medical records were collected, in which the inclusion criteria was the age group above 12 years old and a dermatological pathology as the main complaint, as well as a complete filling of the medical record.

In group 1, the medical records were reviewed to confirm the diagnosis, and were confirmed based on the Hanifin and Rajka Criteria (pruritus, morphotopography compatible with dermatitis in the age group studied, tendency to chronicity or relapse, and personal or family history of manifestations of atopy: asthma, rhinitis, atopic dermatitis). Age, sex, gender, occurrence of allergic rhinitis, asthma, food allergy, and the following comorbidities: obesity, hypertension, depression and active anxiety were investigated as well. To determine the severity of the condition, the SCORAD method (Scoring Atopic dermatitis) [16] was applied; medical records that did not contain the information needed to determine SCORAD were also discarded.

As for the survey of comorbidities in both groups, active pathologies were considered in the inclusion, that is, defined as those that are or are not under pharmacological or non-pharmacological control (asthma, hypertension, depression and anxiety) and that are known to manifest themselves at the presence of any triggering factor (rhinitis, food allergy) or present at the time of consultation (obesity).

Incomplete medical records were discarded from the study in both groups.

The study protocol was approved by the Ethics Committee for independent clinical research, under CAAE n. 35901720.0.0000.5514, Opinion Number: 4,199,207, of July 27, 2020.

4. Results

Between the 127 medical records containing the diagnosis of atopic dermatitis in patients from 12 years of age, 31 were discarded because they did not meet the pre-established assessment criteria, remaining a total of 96 patients whose medical records were considered valid for the study.

Within the atopic group, regarding sex, 65 (67.7%) were female and 31 (32.3%) were male. Regarding the age profile, the average age of the patients was 23.05 +7.47 years (minimum age: 12 years; maximum age: 50 years). Regarding the time of appearance of the symptoms (before or after 12 years old), 71 (74%) had their topical dermatitis diagnosed before 12 years old, and 25 (26%) after this age.

Regarding the severity of AD, 76 (79.2%) manifested the mild form, 18 (18.8%) the moderate form and 2 (2.1%) the severe form.

Of the 180 records collected to compose the control group, 99 were considered valid for the study. The average age in this group was 35.4 + 6.4 years (minimum age: 12 years; maximum age: 74 years); 50 were female and 49 males.

In this group, the most prevalent dermatoses were: melasma (15,1%), acne (14,1%) and telogen effluvium (12,1%), followed by androgenetic alopecia (8%), onychomycosis (8%), contact dermatitis (7%), solar keratosis (4%), seborrheic dermatitis (3%), psoriasis (2%), rosacea (3%), pharmacoderma (2%), basal cell carcinoma (2%), folliculitis (2%) melanocytic nevi (2%), pityriasis versicolor (2%), tinea pedis (2%) and hives (2%); with 1% occurrence: sebaceous cyst, herpes simplex, hidradenitis, lipoma, solar melanosis, vitiligo, stasis dermatitis, perioral dermatitis and seborrheic keratosis.

4.1 Statistical evaluation

As these are non-quantitative variables, the Chi Square test was used, with a 95% confidence interval (significance level: $p < 0.05$).

4.2 Prevalence of atopic diseases

Among the 96 patients evaluated in the atopic group, 34 (35.4%) had atopic comorbidities; in the control group, this percentage was 14%, with a statistically significant superiority ($p < 0.05$).

With regard to allergic rhinitis, 33.3% of group 1 had a history of allergic rhinitis attacks, while in the control group, 7% claimed to have the same disease. ($p < 0.0001$); As for asthma, 17% of group 1 had asthma, while in the control group, only 5% claimed such comorbidity ($p < 0.05$) and, as far as food allergy is concerned, group 1 had 11.5% with this complaint, while in the control group, 4% had a clinical diagnosis of food allergies ($p = 0.05$).

Food allergy in the atopic group has been reported mainly with shrimp, chestnuts, cinnamon and pineapple; in the non-atopic group, it was reported with seafood, peanuts, tomatoes and cod.

The prevalence of atopic comorbidities was higher in the atopic dermatitis group, for all diseases studied, in a statistically significant way, as shown in TABLE 1.

TABLE 1. **Prevalence of other atopic diseases in patients with atopic dermatitis compared to a control group.**

Allergic disease	Group 1 (with AD)	Group 2 (without AD)	p-value
Total of diseases	34 (35,4%)	14 (14,0%)	=0,005
Rhinitis	32(33%)	7 (7,0%)	<0,0001
Asthma	17(17,7%)	5 (5,0%)	=0,005
Food allergy	11(11,5%)	4 (4,0%)	=0,05

In the atopic group, the prevalence of rhinitis and bronchitis was higher in patients with moderate AD (38.9% and 27.8%, respectively); food allergy was more frequent in the mild form of AD (13.2%); (TABLE 2) however, these percentages were not significant for any of the groups, not allowing the correlation of the occurrence of these allergic diseases with the severity of atopic dermatitis. The non-occurrence of atopic diseases in patients with severe form can be explained by the very small size of this group. There was also no greater prevalence of any of the diseases related to sex, age group or onset of the condition (in childhood or after 12 years).

TABLE 2. **Prevalence of other atopic diseases in patients and severity of atopic dermatitis.**

	mild	moderate	severe	p-value
rhinitis	32,90%	38,90%	no	0,534
asthma	15,80%	27,80%	no	0,392
food allergy	13,20%	5,60%	no	0,579

4.3 Cardiovascular comorbidities

Two diseases were investigated: obesity and high blood pressure. In the control group, 21 (21%) had some cardiovascular comorbidity, while in the atopic group this number was 23 (23.9%); there was no statistical difference between the groups.

Obesity was identified in 22.9% of the atopic group and 15.1% in the control group. Although there is a higher prevalence of obesity in the atopic group, there was no statistically significant difference ($p = 0.157$). As for hypertension, the atopic group contained only 1 patient with this disease (1.04%), while in the control group the percentage of hypertensive patients was 7%, with statistically significant superiority ($p = 0.035$).

Within the atopic group, the severity of the condition had no statistically significant correlation with obesity or arterial hypertension, since the only hypertensive patient in this group had mild AD.

4.4 Psychiatric comorbidities

Psychiatric comorbidities, depression and anxiety, under psychotherapeutic or pharmacological treatment at the time of consultation were considered. Within the atopic group, 39% had some psychiatric comorbidity, while in the control group, 34.3% also reported some of the psychiatric diseases, therefore, there was no significant difference between the groups.

Regarding depression, it was present in 13.5% of patients in the atopic group and in 8% of the control group; although there was a higher prevalence in the atopic group, there was no statistically significant difference ($p = 0.210$).

Anxiety was the most frequent comorbidity in both groups: 29.2% in the atopic group and 26% in the control group, respectively; there is no statistically significant difference between groups. ($p = 0.620$)

5. Discussion

Atopic dermatitis is a predominantly childhood disease; only 1 in 5 children with AD persist with the disease after 8 years of age. The factors that seem to be correlated with persistence in adulthood are the early appearance and more serious disease, although there are conflicting results in the literature, especially in relation to other atopic diseases [17].

Atopy comprises the eventual coexistence of 3 allergic diseases mediated by *IgE*: dermatitis, bronchial asthma and allergic rhinitis, being present simultaneously in about 24% of patients [18]. Food allergy is also related to atopy, due to its prevalence in children with AD and since it is also mediated by *IgE* and can cause exacerbations of dermatitis [19,20].

In the sample of patients with atopic dermatitis, all allergic diseases studied - rhinitis, asthma and food allergy - had a higher prevalence, statistically significant, in relation to the control group. The correlation between allergic diseases remaining in adulthood can be partly explained by some findings: alterations of fillagrin in AD increase thymic lymphopoietin (TSPL), a cytokine that favors the perpetuation of the TH3 response in pulmonary epithelium; TSLP generated by keratinocytes, which promotes the production of Th2 lymphocytes in the damaged skin of patients with atopic dermatitis, also seems to favor asthma in an animal model, as well as other systemic allergic diseases [21].

These diseases still manifest in childhood, in the so-called atopic march, with evidence that early-onset AD is a risk factor for the onset of other atopic diseases [5];

The main criticism of atopic march is that relatively few children (3.1%) follow the typical model (initially dermatitis, followed by asthma and then rhinitis); demonstrating that this concept is very restrictive. Thus, a model has been proposed in which atopic march is defined by the initial development of AD followed by any other allergic manifestation or disease [5].

Since it is widely accepted that childhood atopic dermatitis and adult-onset asthma are distinct entities, some authors have proposed that a non-allergic pathophysiological mechanism for adult-onset asthma may exist, which is induced by (age-related) changes in the lungs and the immune system [22].

In our sample, 35.4% of AD patients had allergic comorbidities; a study evaluating 2569 Iranian adults investigated the prevalence of atopic diseases, revealing that the existence of at least one of the allergic diseases was found in 36.3% of cases. Regarding the prevalence of asthma and rhinitis, the data were also similar. In the study cited, rhinitis was present in 28.5% of the studied population, while in the present study, the prevalence was 33%. As for asthma, the prevalence was 7.6% lower than in our sample (17.7%). These data from the Iranian study also demonstrate that, among the general adult population, the most prevalent allergic disease is rhinitis, which coincides with the atopic group of the sample studied here [23].

Another cohort study in 306 patients with atopic dermatitis shows that 36.6% had asthma in adulthood and 61% rhinitis, both of which are significantly larger than the non-atopic group [24]. This predominance of the occurrence of rhinitis appears in other studies, demonstrating its close relationship with atopic dermatitis and its continuity after adulthood [25,26].

In the evaluated sample of adult patients with AD, no significant correlation was observed between the severity of this dermatosis and the occurrence of other atopic diseases, possibly because the persistence of AD in adulthood, or its appearance after childhood, is not related to severity of the case [9].

Food allergy, on the other hand, has figured as an atopic disease, with an increased incidence in the last two decades, and its appearance in childhood follows a curve similar to that of dermatitis in the first 5 years of life [27].

Current evidence indicates that the manifestations of food allergy have no correlation with the severity of atopic dermatitis; which was reaffirmed by the study, in which the population analyzed did not show a correlation between the occurrence of food allergy and the severity of AD.

5.1 Cardiovascular comorbidities

Hypertension and obesity have been linked to atopic dermatitis both in children and in adults; in a meta-analysis of 30 studies, a higher prevalence of these comorbidities was observed in AD patients in the United States and Asia, but not in Europe [28].

In the group of adult patients with AD studied, there was no higher prevalence of hypertension or obesity, when compared to the control group, nor even a higher prevalence related to the intensity of AD.

5.2 Psychiatric comorbidities: anxiety and depression

Another group of comorbidities recently related to atopic dermatitis were some mental illnesses, especially anxiety and depression [9].

Studies show that more than 30% of patients with atopic dermatitis may have psychiatric and psychosocial diseases, which also appears in the results of this research (29.2% of patients in the atopic group) [8,29,30];

In our sample, the non-atopic group also had a high incidence of anxiety (26%), most likely due to the presence of other dermatoses that also cause emotional stress, such as telogen effluvium, acne, melasma and psoriasis, present in 34% of patients in the group control.

Chronic stress has been shown to lead to an increase in 5-hydroxytryptamine 2a receptors on the skin, which results in changes in the skin innervation and increased responsiveness of the sympathetic nervous system, which can also result in exacerbation of the symptoms of dermatitis itself [31]. In our sample, there was also no significant difference between the occurrence of depression or anxiety and the severity of AD.

A study of 5563 American patients showed that adults with AD have a higher rate of short sleep duration, difficulty in reconciling sleep and daytime tiredness, with the majority of this population having the mild form of AD - that is, before the severity itself, sleep deprivation is probably the factor that is most related to anxiety and depression disorders [32,33].

6. Conclusion

In Brazil, allergic comorbidities - asthma, rhinitis and food allergy - showed a higher prevalence in the adult AD population compared to the control group in the same age group; this data must be taken into account when investigating eczematous dermatitis in adults, even when there is no history of atopy in childhood, as some patients may develop AD in adulthood.

Regarding cardiovascular comorbidities, the sample studied did not reveal a correlation between obesity or arterial hypertension with the presence of AD in adults. These findings deserve further investigation, since the sample studied here is small, and the control group contained older patients, who are a risk factor for both diseases studied.

Finally, in relation to psychiatric disorders (anxiety and depression), although there is no significant difference in relation to the control group (where there were other dermatoses that are also related to these psychiatric disorders), the prevalence was shown to be high, coinciding with the literature. These data demonstrate the importance of a more detailed investigation on this group of comorbidities, especially regarding sleep quality, which directly interferes with them and is common in patients with atopic dermatitis, due to the presence of pruritus.

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