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RESEARCH ARTICLE

Interleukin-17A serum levels in young patients with atopic dermatitis and food allergy

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ABSTRACT. ***Background:*** **Atopic dermatitis (AD) is a common skin disorder accompanied by skin barrier disruption. Patients with AD are commonly affected by food allergy.** ***Objectives:*** **The present case–control study aimed to assess interleukin-17A (IL-17A) serum levels in children with AD and food allergies and to determine whether increased serum levels of this inflammatory cytokine correlate with disease severity.** ***Methods:*** **Healthy control subjects and patients were tested for food allergen reactivity by skin prick test and specific, as well as total, immunoglobulin E (IgE) analysis. IL-17A serum levels were measured by enzyme-linked immunosorbent assay technique.** ***Results:*** **Patients with AD had significantly higher median (interquartile range) serum IL-17A (27 pg/mL [20–35]** ***vs.*** **7 pg/mL [4.875–15.25];** $P < 0.001$**) and total IgE levels (190 IU/mL [127–279]** ***vs.*** **26.5 IU/mL [18.75–43.25];** $P < 0.001$**) than controls and 44.6% (37/83) had a positive family history of allergy. Most patients with AD were reactive to two or three food allergens, with milk, eggs and nuts being the most common. No significant correlations were found between IL-17A levels and age and sex of patients, total IgE levels, the number and type of reactive food allergens and disease severity. In the receiver-operating characteristic analysis, the discriminating power of IL-17A and total IgE for AD severity was deficient when used alone but enhanced in combination.** ***Conclusion:*** **Serum IL-17A levels cannot be considered as a reliable AD severity measure and should be combined with other markers in a multimarker technique to enhance its predictive value.**

Key words: allergy, atopic dermatitis, atopy, food allergy, interleukin-17

Atopic dermatitis (AD) is a common chronic inflammatory skin condition characterized by itchy eczema and skin dryness. It usually starts in childhood, although it can affect adults as well [1]. According to the "atopic march" theory, AD is one of a chain of events that can lead to allergies such as food allergies, asthma and allergic rhinitis [2-4]. The pathophysiology of AD is complicated and diverse, with genetic, immunologic and environmental factors all playing a role. Food allergens are one of the environmental factors [5]. Studies documented that food allergies can occur in 20% to 80% of patients with AD [6, 7].

The AD was once thought to be a T-helper 2 (Th2)-mediated illness with high levels of serum immunoglobulin E (IgE). According to research, the Th1, Th22 and Th17 cells are also involved in the etiology of AD [8]. Th17 cytokines such as interleukin-17 (IL-17) and IL-22 have been expressed in AD lesioned skin [9]. There are six members of the IL-17 family (IL-17A through IL-17F) [10]. The first and most studied member, IL-17A (also known as IL-17), has a wide range of biologic actions due to the widespread distribution of its receptor [11]. IL-17A is a pro-inflammatory regulator in various immunologic and inflammatory responses, inducing the release of several cytokines, chemokines, adhesion molecules and growth factors [12]. However, in several models, its involvement in the regulation of IgE-mediated allergic responses is unknown. Studies reported that patients with AD have both decreased [13] and elevated amounts of IL-17 in their peripheral blood [14].

In this context, this study aimed to assess serum levels of IL-17A in children with AD and food allergy and to evaluate IL-17A correlation with AD severity and food allergen reactivity.

Abbreviations

AD	Atopic dermatitis
sIgE	Specific IgE
SPT	Skin prick test
Th2	T-helper 2

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MATERIALS AND METHODS

Subjects and study settings

Sample size estimation was performed by Raosoft statistical package for sample size calculation. To achieve a 95% confidence level and a margin of error of 8%, according to a previous study by Samady *et al.* [15], the expected AD prevalence among children with food allergy is 16.2%. A sample size of 83 subjects per group was enough to achieve the study objective.

This case–control study included 83 patients with AD and food allergy and 83 matched, nonallergic, nonatopic healthy control subjects. The diagnosis of food allergy was established if the patient had a convincing clinical history of an allergic reaction to food in addition to a proven positive skin prick test (SPT) or specific IgE (sIgE) against any food allergen. We confirmed the diagnosis of food allergy in sensitized patients by oral food challenge (OFC) test according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines [16]. Patients on medications (anti-interleukins, oral corticosteroids and antihistaminics) at least 1 week before the test or those with autoimmune disorders, anaphylaxis and severe or unstable asthma were excluded from the study.

AD severity assessment

Each participant was subjected to detailed history taking stressing on family history of allergy and clinical examination. AD severity was assessed using the scoring atopic dermatitis (SCORAD) index using the formula of (A/5 + 7B/2 + C), where A refers to the extent (0–100), B refers to the intensity (0–18) and consists of erythema, edema, dryness, lichenification, excoriations and oozing/crusts and C refers to the subjective symptoms such as daily pruritus and sleeplessness (0–20). The SCORAD mild range is 0 to 15, the moderate range is 16 to 40, the severe range is >40 and the maximum range is 103 [17, 18].

SPT to food allergens

Skin testing was performed [19] using standardized allergen extracts provided by Hamilton (Omega, Allergy OVERSEAS Consultant Inc., Regina, Saskatchewan, Canada). The test was performed using the following food allergens: egg white, egg yolk, tomato, soybean, meat, mango, fish, peanuts, milk, wheat, banana, strawberry, cocoa, chicken, shrimp and hazelnuts. Histamine dihydrochloride (10 mg/mL) was used as a positive control, whereas saline was used as a negative control. Subjects were asked to stop antihistamines a week before skin testing. The largest diameter of the wheal was measured and it was considered positive if it was $\geq$3 mm [20].

Total IgE, sIgE and IL-17 testing

From each participant, 4 mL of blood was taken in a commercially available plain (anticoagulant free) vacutainer and then serum was separated by centrifugation (3500*g* for 20 minutes) and stored at –80°C until further analysis.

According to the manufacturer's instructions, we used the enzyme-linked immunosorbent assay (ELISA) kit (EUROIMMUN AG, Seekamp 31 23560 Lübeck, Germany; Cat No. EV 3840-9601 E) to measure the total IgE levels in the diluted serum samples (1/10) by sample buffer's instructions. Using a microtiter plate ELISA reader (BioTek, Winooski, VT, USA), the measurement wavelength was 450 nm (620–650 nm reference wavelength). The upper limit of the reference range was 155 IU/mL for those aged 6 to 9 years, 199 IU/mL for those aged 10 to 15 years and 100 IU/mL for those aged >16 years.

sIgE assay for food allergens was performed using the immunoblot technique (MEDIWISS Analytic GmbH, Moers, Germany; Art. No.: A0330) with a panel of 30 food allergens following the manufacture's recommendations. Values more than 0.35 IU/L were considered positive.

IL-17A serum level was determined by the human IL-17A ELISA kit (Thermo Fisher Scientific, Wien, Austria, No.: BMS2017) following the manufacture's recommendations. Absorbance wavelength was read at 450 nm as the primary wavelength using a microtiter plate ELISA reader (BioTek). The results were expressed in pg/mL.

Statistical analysis

All analyses were performed using SPSS 26 program. The Shapiro–Wilk test determined normality. Continuous variables had medians and interquartile ranges, whereas categorical variables had numbers and percentages. The Kruskal–Wallis and Mann–Whitney tests compared sets of quantitative variables. For categorical variables, the Chi-squared or Fisher exact test was used. Cutoff values for identifying patients with different disease severity were determined using receiver-operating characteristic (ROC) analysis. Spearman's rank correlation coefficient evaluated other parameter associations with IL-17A serum levels. A *P*-value of 0.05 or less is significant.

RESULTS

Our study included 83 patients with AD and 83 healthy control subjects. In terms of age, patients with AD were significantly older than controls; their median (interquartile range [IQR]) age was 13 (9–22) years *vs.* 9 years (7–10), respectively, with a *P*-value of <0.001. We found no significant difference between the study and control groups as regards sex. The patients with AD had significantly higher median (IQR) IL-17A (27 pg/mL [20–35] *vs.* 7 pg/mL [4.875–15.25]; $P < 0.001$) and total IgE levels (190 IU/mL [127–279] *vs.* 26.5 IU/mL [18.75–43.25]; $P < 0.001$) than controls. Of all the included AD cases, 44.6% (37/83) had a positive family history of allergy, whereas no one in the control group did. Characteristics of both groups are presented in *table 1*.

The majority of the patients with AD had mild disease severity (43.4%, 36/83) and no associated atopic disorders (57.8%, 48/83). Allergic rhinitis and asthma were the most common accompanying atopy in 21.7% (18/83) and 9.6% (8/83) of the patients with AD,

Table 1
Characteristics of the included patients with AD *vs.* the controls.

Characteristic		AD cases (n = 83)	Control (n = 83)	P-value
Age (years)	Median (IQR)	13 (9–22)	9 (7–10)	**<0.001**
Sex, n (%)	Male	35 (42.2%)	33 (39.8%)	0.802
	Female	48 (57.8%)	50 (60.2%)	
Family history of allergy, n (%)	Negative	46 (55.4%)	83 (100.0%)	**<0.001**
	Positive	37 (44.6%)	0.0 (0.0%)	
Total IgE (IU/mL)	Median (IQR)	190 (127–279)	26.5 (18.75–43.25)	**<0.001**
IL-17A (pg/mL)	Median (IQR)	27 (20–35)	7 (4.875–15.25)	**<0.001**

AD: atopic dermatitis; IgE: immunoglobulin E; IL-17A: interleukin-17A; IQR: interquartile range. Significance was set at <0.05.
Significant P-values are in bold

respectively. Most patients with AD were reactive to two or three food allergens in sIgE testing (41.0%, 34/83 and 33.7%, 28/83, respectively) and the SPT (34.9%, 29/83 and 38.6%, 32/83, respectively). In the SPT, patients with AD were reactive mainly to milk (44.6%), eggs (36.1%) and nuts (30.1%). In addition, in the sIgE analysis, most patients with AD showed reactivity to milk (44.6%), egg white (36.1%), egg yolk (32.5%), flour (27.7%) and nuts (27.7%). Clinical characteristics of the included patients with AD are summarized in *table 2*.

Comparing the patients with AD according to SCORAD index, we could not detect any significant differences ($P > 0.05$) regarding age, sex, serum levels of IL-17A and total IgE, associated atopic disorders and family history of allergy. Of the severe AD cases, 21.4% (3/14) and 35.7% (5/14) were reactive to four food allergens in sIgE testing and the SPT, respectively. In addition, the egg was the only allergen that showed significant differences between the three severity groups ($P = 0.016$) associated with severe disease (57.1%, 8/14; *table 3*).

We could not detect any significant correlations between the IL-17A levels and age of patients, total IgE levels, the number of reactive food allergens either in the sIgE or in the SPTs (*table 4*).

Also, in the patients with AD, we found no significant differences by comparing levels of IL-17A according to the sex, family atopy history and positive food allergens in the SPT (*table 5*).

In the ROC analysis, the discriminating power of IL-17A and total IgE for AD severity was deficient (area under the curve [AUC] 0.5) when used alone but enhanced when they were used together. To distinguish between mild and moderate/severe AD and moderate and severe AD, the AUC was increased to 0.810 and 0.742, respectively (*figure 1*).

DISCUSSION

The AD is an inflammatory skin disorder that affects up to 20% of children and 2% to 5% of adults globally [21, 22]. It is characterized by skin barrier disruption mediated by hereditary factors, immunologic dysregulation and skin microbiome imbalance. Food allergy is common in patients with temporary skin barrier disruption in a process called (the atopic march) [23]. One-third of severe AP patients had positive symptoms on an OFC, with up to half of patients displaying positive food sIgE [4]. Many studies have investigated the role of IL-17A in the course of atopic disorders [24, 25], however, yielded conflicting results.

Up to our knowledge, there are not enough studies in pediatrics that investigated the role of IL-17A in patients with AD with food allergy. By conducting this case–control study, we aimed to gain insight into IL-17A levels in children suffering from AD and food allergy and the correlation of IL-17A with total serum IgE level and AD severity by including 83 children with AP associated with food allergy and 83 healthy controls.

In our study, 44.6% of the included patients with AD had a positive family history of allergies. In a study by Saeki *et al.* [26], most patients with AD had atopic diatheses such as a family history of allergic diseases or history of asthma, rhinitis, or conjunctivitis. Several other studies have investigated the effect of family history of allergy on AD development and course [27, 28]. Böhme *et al.* [29] found that AD developed in 27.1% of children without atopic family history and up to 50.0% of children with atopic family history with no difference in the impact between the maternal and paternal atopic history. Similarly, Alford *et al.* [30] revealed that parental AD history patterns could influence the disease experience of their children, including characteristics such as onset age, disease persistence and severity.

Vaneckova and Bukač [31] have suggested that although IgE plays a role in allergic rhinitis and asthma, there is no evidence that IgE plays a role in AD development. Other studies showed that IgE binds to basophils and mast cells, causing the release of critical cytokines in allergic reactions [32, 33].

Our study showed that total IgE serum levels were significantly elevated in the AD group than in the controls. Hu *et al.* [34], in their study of the clinical relevance of serum IgE in patients with AD, found similar results and stated that extrinsic (allergic) AD, which is characterized by high total serum IgE levels and positive sIgE for food allergens, was more predominant than intrinsic (nonallergic) AD, characterized by normal total IgE levels and no sIgE or skin barrier dysfunction. They also reported that the prevalence of extrinsic AD was significantly higher

Table 2
Clinical characteristics of the AD cases (n = 83).

Characteristic		AD cases (n = 83)
Number of positive sIgE food allergens, n (%)	1	17 (20.5%)
	2	34 (41.0%)
	3	28 (33.7%)
	4	4 (4.8%)
Number of positive sIgE food allergens, n (%)	Milk	37 (44.6%)
	Shrimp	18 (21.7%)
	Fish	19 (22.9%)
	Strawberry	18 (21.7%)
	Egg yolk	27 (32.5%)
	Egg white	30 (36.1%)
	Flour	23 (27.7%)
	Banana	14 (16.9%)
	Mango	12 (14.5%)
	Nuts	23 (27.7%)
Number of positive food allergens in SPT, n (%)	1	16 (19.3%)
	2	29 (34.9%)
	3	32 (38.6%)
	4	6 (7.2%)
SPT-positive food allergens, n (%)	Milk	37 (44.6%)
	Fish	20 (24.1%)
	Strawberry	17 (20.5%)
	Egg	30 (36.1%)
	Wheat	23 (27.7%)
	Banana	13 (15.7%)
	Solanaceae	17 (21.0%)
	Nuts	25 (30.1%)
	Mango	13 (15.7%)
SCORAD index, n (%)	Mild	36 (43.4%)
	Moderate	33 (39.8%)
	Severe	14 (16.9%)
Associated atopic disorders, n (%)	None	48 (57.8%)
	Allergic conjunctivitis	3 (3.6%)
	Asthma	8 (9.6%)
	Allergic rhinitis	18 (21.7%)
	Chronic urticarial	3 (3.6%)
	Allergic conjunctivitis + Allergic rhinitis	1 (1.2%)
	Allergic rhinitis + Chronic urticarial	2 (2.4%)

AD: atopic dermatitis; SCORAD: scoring atopic dermatitis; sIgE: specific IgE; SPT: skin prick test. Significance was set at <0.05.

in the adolescent group 90.2% than in the elderly (73.9%).

In terms of AD severity determined by the SCORAD index, we found no significant differences in total IgE serum levels or atopic family history. Vaneckova and Bukač [31], on the other hand, reported a strong link when they discovered that in patients with severe AD, 93% had total IgE levels >200 IU/mL and 66% had a positive family history of atopy.

Regarding our included patients with AD, their median (IQR) age was 13 years (9–22): 57.8% were females, 43.4% were mild cases and 39.8% and 16.9% were moderate and severe cases. Comparatively, of the 867 children (aged 5.9 ± 3.6 years with 50.5% females) affected by AD included in a study by Geat *et al.* [18], 41.2% had mild AD, 43.6% had moderate AD and 15.2% had severe AD. Moreover, in a study on 296 children with AD aged ≥14 years, Celakovská and Bukač [32] discovered that the mild, moderate and severe AD frequencies were 14%, 38% and 6%, respectively, in children with a positive family history of allergy. On the other hand, among those with no family history, AD frequencies were 18%, 21% and 3%, respectively. The low frequency of severe disease could be explained by the young age and female predominance of the included patients.

Bantz and colleagues [23] reported that the lack of dermal integrity is considered the primary mechanism of allergic sensitization and development of the atopic march. AD is the first step and allergic rhinitis and asthma are the endpoints. They also reported that it is common for those with early onset, severe and persistent atopic eczema to have food allergies.

Furthermore, in a study by Park and colleagues [35], they reported that children with multiple food allergies mainly were atopic, with 56% having AD, 47% having allergic rhinitis and 38% having asthma.

Most of our studied patients with AD were allergic to two or three types of food: with cow's milk, eggs and nuts being the most common sensitizing allergens. Only egg allergen reactivity was significantly associated with disease severity (P = 0.016). Reactivity for four food allergens was more frequent in the severe group. In our study, 61.1% of the mild and 66.7% of the moderate patients experienced no other associated atopic disease compared to 28.6% only of severe patients but with no statistical significance.

Furthermore, in our study, eight (22.2%), five (15.2%) and five (35.7%) patients of the mild, moderate and severe groups, respectively, suffered from allergic rhinitis, whereas asthma was found in two (5.6%), three (9.1%) and three (21.4%) patients, respectively. Likewise, Celakovská and Bukač [32] reported that the incidence of bronchial asthma in mild, moderate and severe AD was 35%, 45% and 64%, respectively, whereas the incidence of allergic rhinitis was 65%, 76% and 96%, respectively.

Similarly, of the highly atopic children included in Sampson and Ho [36], 100% had AD, 50% had allergic rhinitis or asthma and 57% had a food allergy to two or three foods. Few children showed reactions to more than three allergens. They also stated that five foods, that is, egg, peanut, milk, wheat and soy, were responsible for about 60% of positive reactions. In addition, Celakovská and Bukač [37] reported that bronchial asthma, allergic rhinitis and chronic eczematous lesions are more common in patients with AD with food allergies to common foods such as wheat soy, peanuts, egg and milk.

Consistent with our results is a case–control study by Estrada–Reyes and colleagues [27] in which they

Table 3
Comparison between patients with atopic dermatitis according to the scoring atopic dermatitis index.

Characteristic		Mild (n = 36)	Moderate (n = 33)	Severe (n = 14)	P-value
Age (years)	Median (IQR)	11.5 (8.25–18.5)	17 (9–26)	12 (10.75–18.25)	0.240
Sex, n (%)	Male	11 (30.6%)	16 (48.5%)	7 (50.0%)	0.172
	Female	25 (69.4%)	17 (51.5%)	7 (50.0%)	
Total IgE (IU/mL)	Median (IQR)	200.5 (123.25–300.75)	190 (135–282.5)	183 (127–213.75)	0.824
IL-17A (pg/mL)	Median (IQR)	28 (20–35.75)	24 (20.5–35)	24 (17.25–38.5)	0.755
Associated atopic disorders, n (%)	None	22 (61.1%)	22 (66.7%)	4 (28.6%)	0.423
	Allergic conjunctivitis	1 (2.8%)	2 (6.1%)	0 (0.0%)	
	Asthma	2 (5.6%)	3 (9.1%)	3 (21.4%)	
	Allergic rhinitis	8 (22.2%)	5 (15.2%)	5 (35.7%)	
	Chronic urticarial	1 (2.8%)	1 (3.0%)	1 (7.1%)	
	Allergic conjunctivitis + Allergic rhinitis	1 (2.8%)	0 (0.0%)	0 (0.0%)	
	Allergic rhinitis + Chronic urticarial	1 (2.8%)	0 (0.0%)	1 (7.1%)	
Number of positive sIgE food allergens, n (%)	1	9 (25.0%)	4 (12.1%)	4 (28.6%)	**0.010**
	2	18 (50.0%)	12 (36.4%)	4 (28.6%)	
	3	9 (25.0%)	16 (48.5%)	3 (21.4%)	
	4	0 (0.0%)	1 (3.0%)	3 (21.4%)	
Number of positive food allergens in SPT, n (%)	1	9 (25.0%)	3 (9.1%)	4 (28.6%)	**<0.001**
	2	13 (36.1%)	12 (36.4%)	4 (28.6%)	
	3	14 (38.9%)	17 (51.5%)	1 (7.1%)	
	4	0 (0.0%)	1 (3.0%)	5 (35.7%)	
SPT-positive food allergens, n (%)	Milk	17 (47.2%)	16 (48.5%)	4 (28.6%)	0.415
	Fish	8 (22.2%)	7 (21.2%)	5 (35.7%)	0.535
	Strawberry	7 (19.4%)	7 (21.2%)	3 (21.4%)	0.979
	Egg	7 (19.4%)	15 (45.5%)	8 (57.1%)	**0.016**
	Wheat	10 (27.8%)	8 (24.2%)	5 (35.7%)	0.724
	Banana	5 (13.9%)	8 (24.2%)	0 (0.0%)	0.104
	Solanaceae	5 (13.9%)	7 (21.2%)	5 (35.7%)	0.226
	Nuts	13 (36.1%)	9 (27.3%)	3 (21.4%)	0.537
	Mango	5 (13.9%)	6 (18.2%)	2 (14.3%)	0.876
sIgE-positive food allergens, n (%)	Milk	16 (44.4%)	13 (39.4%)	8 (57.1%)	0.534
	Shrimp	9 (25.0%)	7 (21.2%)	2 (14.3%)	0.709
	Fish	10 (27.8%)	7 (21.2%)	2 (14.3%)	0.569
	Strawberry	9 (25.0%)	6 (18.2%)	3 (21.4%)	0.790
	Egg yolk	8 (22.2%)	13 (39.4%)	6 (42.9%)	0.209
	Egg white	10 (27.8%)	14 (42.4%)	6 (42.9%)	0.381
	Flour	9 (25.0%)	9 (27.3%)	5 (35.7%)	0.747
	Banana	7 (19.4%)	6 (18.2%)	1 (7.1%)	0.561
	Mango	5 (13.9%)	5 (15.2%)	2 (14.3%)	0.989
	Nuts	11 (30.6%)	10 (30.3%)	2 (14.3%)	0.469
Family history of allergy, n (%)	Negative	21 (58.3%)	18 (54.5%)	7 (50.0%)	0.861
	Positive	15 (41.7%)	15 (45.5%)	7 (50.0%)	

IgE: immunoglobulin E; IL-17A: interleukin-17A; IQR: interquartile range; sIgE: specific IgE; SPT: skin prick test. Significance was set at <0.05
Significant P-values are in bold

discovered that hen egg had the highest rate of SPT positivity, followed by cow's milk, fish and soy. But in contrast to us, they observed no significant difference in the family history of allergic diseases between cases and controls.

Serum levels of IL-17A in our patients with AD were significantly higher than controls but were not significantly associated with AD severity, total IgE levels, patients' sex or type and the number of reactive food allergens. In addition, in ROC curve analysis, IL-17A

Table 4
Correlations of IL-17A with age and total IgE levels in the studied patients with atopic dermatitis (n = 83).

Variable	IL-17A	
	rs	*P*-value
Age	0.053	0.635
Total IgE	0.071	0.523
Number of positive sIgE food allergens	–0.082	0.659
Number of positive food allergens in SPT	–0.187	0.314

IgE: immunoglobulin E; IL-17A: interleukin-17A; rs: Spearman's rank correlation coefficient; sIgE: specific IgE; SPT: skin prick test. Significance was set at <0.05

had a poor predictive ability for the severity of the disease that increased when IL-17A was combined to total IgE.

Partially similar to our results, in a study on 181 children with atopic eczema/dermatitis disorder, Leonardi *et al.* [38] found that IL-17 concentrations were significantly higher in the patients with AD than healthy controls and were significantly positively correlated with the SCORAD index and total IgE levels in serum. Another study by Eyerich *et al.* [39] discovered that more IL-17-producing cells invaded the atopy patch test location than in healthy skin. Furthermore, when Tan *et al.* [40] compared AD children to healthy control subjects regarding IL-17 expression in the skin and serum using immunohistochemistry and ELISA techniques, respectively, they found that IL-17 expression levels in the skin, but not in the serum, were significantly higher in patients with AD than controls.

In contrast to our findings, many other studies revealed a strong link between AD symptom intensity and IL-17 levels, proposing it as a significant biomarker of AD severity. As a pro-inflammatory cytokine, IL-17 was thought to be implicated in the process of skin inflammation in AD [14, 41].

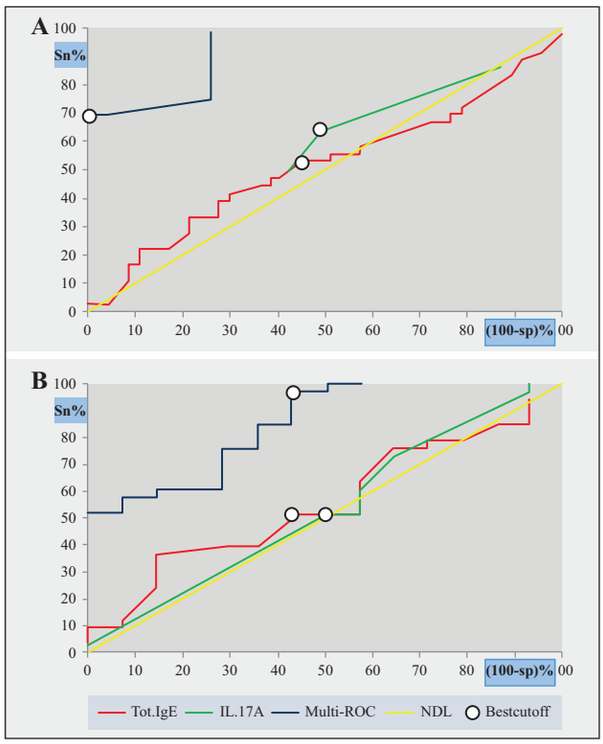
IL-17 regulates tissue inflammation and affects innate immunity by increasing chemokines and pro-inflammatory cytokines [42]. It can activate allergen-specific Th2 cells, increase eosinophils and neutrophils and generate serum IgE [43-45]. Amin *et al.* [46] also confirmed that IL-17a increases IgE production and that IgE levels drop after Th17 cells from allergic patients are depleted *in vitro*, which contrasts our study in which IL-17A had no significant correlation with total IgE serum levels.

IL-17a-producing cells are observed in high numbers in the peripheral blood of allergic people [47]. IL-17 has

Table 5
Interleukin-17A levels according to sex and family history of the included patients with atopic dermatitis as well as the different food allergen reactivity.

Variable		IL-17A level				*P*-value
		n	Median	IQR		
Sex	Females	48	27	19.25	37.5	0.729
	Males	35	25	20	35	
Family history	Neg	46	28.5	18	38	0.488
	Pos	37	24	20	35	
Cow milk	Neg	46	25	19	35.25	0.595
	Pos	37	29	20	35	
Fish	Neg	63	25	20	35	0.394
	Pos	20	30.5	19.75	37.5	
Strawberry	Neg	66	27	20	35	0.892
	Pos	17	25	19.5	36.5	
Egg	Neg	53	27	19	35	0.537
	Pos	30	26	22.75	36	
Wheat	Neg	60	28	20	36	0.258
	Pos	23	24	19	35	
Banana	Neg	70	25	19.75	36	0.97
	Pos	13	28	21.5	33.5	
Solanaceae	Neg	64	27	22	35	0.839
	Pos	17	35	18	39	
Mango	Neg	70	27	20	35.25	0.429
	Pos	13	24	18.5	35	
Nuts	Neg	58	24.5	18	35	0.348
	Pos	25	28	21	35.5	

IL-17A: interleukin-17A; IQR: interquartile range; Neg: negative; Pos: positive. Significance was set at <0.05



Variable	Mild vs. Moderate/severe AD						
	Cut-off	AUC (95% CI)	SP%	SN%	PN%	PP%	Eff%
Total IgE	200 IU/mL	0.516 (0.390-0.641)	55.3	52.8	60.5	47.5	54.2
IL-17A	24 pg/mL	0.324 (0.205-0.442)	51.1	63.9	64.9	50.0	56.6
Total IgE at 200 IU/mL+ IL-17A at 60		0.810 (0.714-0.906)	100.0	69.1	81.1	100.0	86.7
Variable	Moderate vs. Severe AD						
	Cut-off	AUC	SP%	SN%	PN%	PP%	Eff%
Total IgE	188 IU/mL	0.486 (0.303-0.668)	57.1	51.5	33.3	73.9	53.2
IL-17A	24 pg/mL	0.463 (0.283-0.643)	50.0	51.5	30.4	70.8	51.1
Total IgE at 188 IU/mL + IL-17A at 38		0.742 (0.617-0.867)	57.1	97.0	88.9	84.2	85.1

Significance was set at <0.05

Figure 1
ROC curve analysis showing the diagnostic performance of total IgE and IL-17A and their combination for discriminating **(A)** mild from moderate/severe AD patients; and **(B)** moderate from severe patients with AD.

been linked in animal models to asthma and AD; only a few studies have identified increased expression of IL-17a in allergic humans [14, 48]. Some researchers have discovered a deficiency of IL-17a and IL-23, a Th17 differentiation cytokine, in the skin of patients with AD, which could be explained by the occurrence of skin infections [49].

To sum up, in our study, despite serum levels of IL-17A increased in patients suffering from AD with food allergy than controls, their concentrations in blood did not reflect the severity of the disease and had poor predictive power. Combined detection of IL-17A together with total IgE improved the predictive ability for disease severity.

In conclusion, IL-17A should not be used alone as a marker for AD severity. To improve IL-17A predictive value, IL-17A should be supplemented with additional markers in a multimarker method or combined severity prediction score.

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