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Correlation between Interleukin 31 and clinical manifestations in children with atopic dermatitis: an observational study

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Abstract
Background: Itching is one of the major and mandatory signs of atopic dermatitis (AD) in children. Interleukin 31 (IL-31) is strongly involved in the genesis of pruritus. In our study, 68 patients aged 0-18 years with proven AD were followed clinically. The role of IL-31 in pruritus as clinical manifestation of AD is known but its etiopathogenetic mechanism is not well known.
Methods: Serum was collected from 31 patients with moderate and severe forms of AD to determine IL-31 and its correlation with activity and severity of the disease. We also studied 30 healthy patients to compare the results of determinations. The IL-31 value was determined using the sandwich enzyme-linked-immunosorbent serologic assay (two antibodies assay). The IL-31 values were expressed as picograms per milliliter (pg/mL) and compared with activity and severity of the disease.
Results: The IL-31 value was much higher in patients with AD compared to the control group. The mean value of findings was 1600 pg/mL compared to the control group with an average of 220 pg/mL. The IL-31 values were positively correlated with the severity and activity of the disease.
Conclusions: The results of our pediatric study established the involvement of IL-31 in the pathophysiology of AD. IL-31 could be a marker of AD track.
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Introduction

Atopic Dermatitis (AD) is a complex chronic inflammatory skin disease that manifests itself in various clinical forms. The prevalence of AD is increasing worldwide and especially in developed countries, and is found in 15–30% of children and 2–10% of adults.[1] The role of Interleukin 31 (IL-31) in pruritus as a clinical manifestation of AD is known but its etiopathogenetic mechanism is not well known. The purpose of this study was to highlight the link between clinical manifestations of AD and increased IL-31 levels; we explained the etiopathogenetic mechanism and identified new possible targets in AD.[1-3] The etiopathogenetic mechanisms of the disease include dysfunction of the immune system with the prepotency of T helper type 2 (TH2) cells, increase in the amount of immunoglobulin E (IgE). Another important mechanism is the dysfunction of epidermal barrier. Antigens penetrate through this defective barrier, thereby producing inflammatory cytokines. Genetic research has demonstrated that certain mutations in the *filaggrin* gene play a prominent role in the occurrence of AD. The microbiota seems to be a factor in shaping the manifestations of AD. An important clinical manifestation of AD is pruritus (intense itching). It was previously believed that histamine and neuropeptides play an important role in the onset of pruritus. However, recent evidence suggests that IL-31 is the most important factor in pruritic responses.[4] IL-31 is produced by activated Th cells, especially Th 2, but also by mast cells, macrophages, and dendritic cells. More recently, eosinophils have become a source of these cytokines, as are basophils that have expressed IL-31 receptors on their surface.[5] IL-31 receptors have also been found in keratinocytes. The receptors for IL-31 are IL-31RA and oncostatin M (OSMR-β). IL-31 has also been presented to have an immunomodulatory role, especially in supporting Th 2-type immunity, which induces the production of IgE found in autoimmune diseases such as bullous pemphigoid, psoriasis, and dermatomyositis. IL-31 belongs to the glycoprotein 130 (gp 130) class of cytokine receptors. It is a part of IL-6 cytokine family and has four spirals that represent a strong ligand for heterodimeric IL-31RA receptor. Oncostatin M receptors are distributed in various cells, including T cells, keratinocytes, eosinophils, basophils, and macrophages.

Interleukin 31 is an important factor in itching and inflammation of the skin as well as in affecting the barrier function, especially by remodeling the tissue induced by IL-31. It also controls other biological functions such as immunomodulatory effect by releasing chemokines, proinflammatory cytokines, regulating cell proliferation, and stimulating itchy sensory neurons dorsal root ganglion (DRG) that induce pruritus. Interest in IL-31 concerning skin diseases refers mainly to pruritus and inflammation and impaired barrier function.[6,7] Epidermal keratinocytes are an important target of IL-31 and some conducted studies have demonstrated that they can cause epidermal proliferation of basal cells. The change in barrier function occurs by decreasing the expression of filaggrin protein and by mutations in the gene that encodes it. Some recent studies have demonstrated that IL-31 may be involved in autoimmune diseases with manifestations especially at the skin level (lupus, dermatomyositis, and alopecia areata).[5,8,9]

Atopic dermatitis is more common in children, begins around the age of 2 months, and continues to affect them until adolescence. The impact of skin manifestations and itching is greater in children.[5] According to BioVendor group, 60% of cases of AD are diagnosed in the first year and 85% up to 5 years of age.[10] It is estimated that 10–30% patients continue to indicate signs of AD even in adult life. Considering the life quality of children with AD, a longitudinal cohort study, including 13,988 children, has proved a nearly 50% higher odds of experiencing sleep-quality disturbances in children with active AD.[11] A 2019 meta-analysis established that 44% patients with AD were more likely to exhibit suicidal ideation and up to 36% more likely to attempt suicide compared with patients without AD.[12]

Materials and Methods

We performed an observational study in the Pediatrics II clinic during 2017–2019 with 68 patients, aged between 0 and 18, with proven AD followed clinically. Approval of the ethics committee and informed consent of each patient were obtained. Inclusion criteria were that patients must be aged 0–18 years, and diagnosed with active AD. The children included in this study were diagnosed for active AD by a pediatrician having specialization in allergology and immunology and a dermatologist. The serum levels of IL-31 were determined using the sandwich enzyme-linked-immunosorbent serologic assay (ELISA with two antibodies).

Diagnostic criteria were the major criteria, which included pruritus as a major sign along with specific skin lesions. Minor signs included history flexural lesions (elbow fold, popliteal fossa, periareolar, and lateral cervical region), personal history of asthma or rhinitis, history of xerotic skin during the last year, and the onset of clinical manifestations at the age of less than 2 years. For the diagnosis of AD, the patient must present the major criterion and three or more minor criteria. Exclusion criteria were acute infectious diseases, other autoimmune diseases, cutaneous manifestations in other diseases, and lack of informed consent.

We evaluated the severity of AD in the patients included in the study using the Severity Scoring of Atopic Dermatitis (SCORAD) index. The objective SCORAD index evaluates the presence and severity of lesions (erythema, edema, crusts, abrasions, lichenification lesions, and cutaneous xerosis) as well as the assessment of the intensity of pruritus and sleep disorders on a scale of 1–10. Depending on the score obtained, AD falls into the following forms of severity:

- <15—light form of AD
- 15–40—moderate form of AD
- >40—severe form of AD

In order to assess the severity of pruritic manifestation, we used a visual analogue scale (VAS) of itching, with score of 1–10.

We determined the value of IL-31 in cases with moderate and severe forms of AD in 31 children. We also used a group of 30 healthy children (control group) who had

the characteristics of the studied group (age, sex, and clinically healthy). The control group consisted of volunteer patients who had presented at our clinic for other reasons.

We also determined total IgE, specific IgE, and eosinophils in the mentioned children groups.[13-15]

Results

The evaluated parameters of the 68 patients included in the study are provided in Table 1, and the parameters evaluated according to age are shown in Table 2.

Visual analogue scale of itching was used with the following results:

VAS = 0: no pruritus—15 patients
VAS < 3: mild pruritus—22 patients
VAS ≥ 3-<7: moderate pruritus—21 patients
VAS ≥ 7-<9: severe pruritus—8 patients
VAS ≥ 9: very severe pruritus—2 patients

In patients aged 0–4 years, VAS scale was calculated collaborating with their parents, who were instructed to note the following clinical manifestations associated with pruritus: agitation, uncontrolled crying, scratching to injury, and sleep disturbance.

The IL-31 value was expressed as picograms per milliliter (pg/mL) and is much higher in patients with AD compared to the control group. The average value of determinations was 1600 pg/mL compared to the control group with an average of 200–290 pg/mL (Figures 1 and 2).

Table 1 Evaluation of the severity of atopic dermatitis through the SCORAD questionnaire.

SCORAD index	P = 0.002
Mild	37 (54.4%)
Moderate	23 (33.8%)
Severe	8 (11.7%)
SCORAD index (average value)	21.4 ± 10.4

The result was a positive correlation between IL-31 values and VAS score because IL-31 was significantly higher in patients with acute manifestations of the disease. The severity of AD increases with time, sometimes in spite of correct therapies, so IL-31 has been correlated with the severity of the disease. There is also a statistically significant correlation between total IgE and IL-31 values.

Discussion

Improving the quality of life by reducing, improving, or eliminating clinical manifestation of AD is the goal for both patient and physician. Good quality of life is achieved by knowing the mechanisms of disease and targeted therapeutic intervention. The association of allergic conditions could affect the quality of life.[4] AD has psychological implications through the appearance of rashes; fortunately, in the children of our study mild and moderate forms of AD predominated. Severe forms of AD, although fewer, have a major impact on the social integration of children.[11] These severe forms must be addressed through the collaboration of pediatrician, allergist, dermatologist, psychiatrist, and psychologist.[12] A comparative analysis of quality of life by age group in our study demonstrated that the age group of 5–9 years predominated, followed by the group of 10–18 years. The most worrying clinical manifestation of AD is itching. This clinical manifestation had a negative impact on the quality of life through both scratching injuries and frequent need to scratch, causing night awakening.[16] IL-31 findings made in 31 children with moderate and severe forms demonstrated that values were much higher than the control group values. The findings were determined by sandwich ELISA and expressed as pg/mL. In the present study, the average value in patients was 1600 pg/mL. In the control group, the IL-31 values were between 200 pg/mL and –290 pg/mL, which are within the normal limits. These results established a correlation between IL-31 values and the activity of the disease.

Blocking of IL-31 receptors was an important target in managing the clinical manifestations of AD, especially pruritus. Nemolizumab is a humanized monoclonal antibody against IL-31 receptors with promising results. A randomized, double-blind, placebo-controlled phase I/Ib clinical trial of nemolizumab concluded that its single subcutaneous

Table 2 Characteristics of the studied group (age, sex, and association with other autoimmune diseases).

Variables	0–4 years	5–9 years	10–18 years
Number of patients	45 (66.1%)	14 (20.5%)	9 (13.2%)
Age (average ± SD)	1.94 ± 0.96	7.08 ± 1.38	13.12 ± 1.32
Gender			
Male	30 (66.6%)	6 (42.8%)	5 (55.5%)
Female	15 (33.3%)	8 (57.2%)	4 (44.5%)
Atopy			
Only atopic dermatitis	30 (66.6%)	6 (42.8%)	4 (44.5%)
Atopic dermatitis associated with other allergic diseases	15 (33.3%)	8 (57.2%)	5 (55.5%)

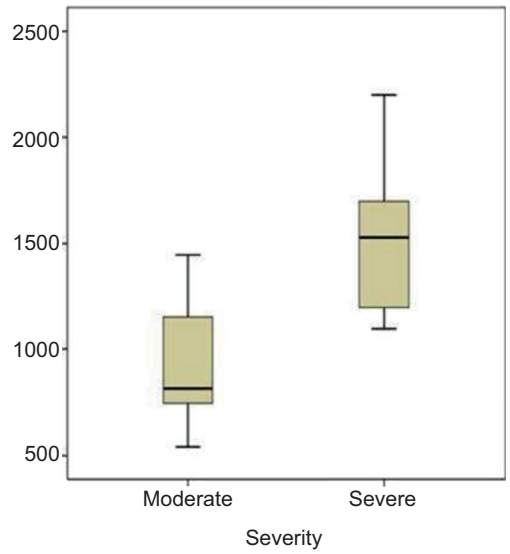

Figure 1 Correlation between IL-31 and the severity of atopic dermatitis.

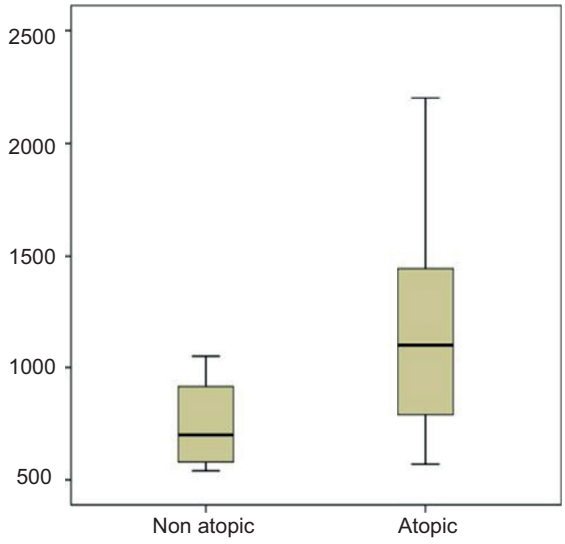

Figure 2 Association between IL-31, atopy (atopic dermatitis), and other allergic manifestations (non-atopic).

administration was well tolerated, and it along with hydrocortisone decreased pruritus manifestations and sleep disturbances in patients with AD.[17]

Conclusion

Role of IL-31 is high in moderate and severe forms of AD. Elevated levels of this cytokine could be a marker of disease activity. Biological treatment (immunotherapy) of AD with IL-31 antagonists is a perspective in the management of allergic manifestations, especially pruritus.

Author Contribution

All authors contributed equally.

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