The value of eosinophilic cationic protein in adults with atopic dermatitis: a research study

KEY WORDS
- Atopic dermatitis
- Inflammatory process
- Person-centered
- Wound care

Aim: To date, the search for diagnostic markers of atopic dermatitis (AD; also known as atopic eczema) is ongoing. Such markers should help to identify allergic inflammation and help control the severity of the disease. Our aim was to analyse the diagnostic significance of eosinophilic cationic protein (ECP) in AD patients. **Methods**: People with AD and those without ('healthy') were examined. AD patients were grouped by age: 18–40 years and >40 years old. All AD patients were tested for allergic inflammation makers. Statistical processing of the obtained results was carried out using variational statistics and the Statistica v10. **Results**: A total of 24 patients with AD and 10 healthy people were included. In the AD group, there were 12 people aged 18–40 years, and 12 people aged >40 years of age. With increased age, there was a decrease in the number of people with the extrinsic form of AD indicated by a high level of IgE, and an increase in the number of people with intrinsic AD indicated by a low level of IgE (odds ratio [OR]: 2.92; 95% confidence interval [CI]: 1.83 to 4.65; $p<0.001$). Both the form of AD and the total serum IgE level were dependent on the age of the patient (OR: 5.72; 95% CI: 2.52 to 13.94; $p<0.001$). Simultaneously, when the severity of AD increased, ECP level increased (OR: 4.26; 95% CI: 2.01 to 9.05). **Conclusion**: We suggest the level of ECP in people with AD could be used as an indicator for allergic inflammation, as the levels of ECP increased with the severity of the disease. The level of ECP did not depend on the age of the patient or the the form of AD.

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The incidence of atopic dermatitis (AD; also known as atopic eczema) has not significantly changed in the last decade, despite advances in the treatment of the disease (Kowalska-Olędzka et al, 2019). According to epidemiological data, AD is a "worldwide phenomenon" affecting 20% of children and adults (Jaworek et al, 2019). The literature's analysis shows that the "schematics" and the standard management of patients with AD do not allow the full necessary therapeutic and diagnostic measures (Eichenfield et al, 2017). As there are no specific diagnostic laboratory markers of AD, the clinical diagnosis of the disease is based on the anamnestic data of the patient, specific clinical symptoms, and the exclusion of other non-inflammatory skin diseases.

The pathogenesis of AD is multifactorial and presumably depends on the interaction of genetic, immunological, environmental and infectious factors, which lead to inflammation and the disturbance of the skin barrier; however, these factors continue to be studied (Rutkowski et al, 2014). The mechanism of disease development distinguishes between immunoglobulin E (IgE)-mediated and non-IgE-mediated AD. AD can be exogenous (external) and endogenous (internal). The literature indicates that 10–45% of patients with endogenous (intrinsic AD) are characterised by low serum IgE and the absence of allergen-specific IgE. Scientists believe that laboratory data for the diagnosis and assessment of the severity of the disease are not specific or

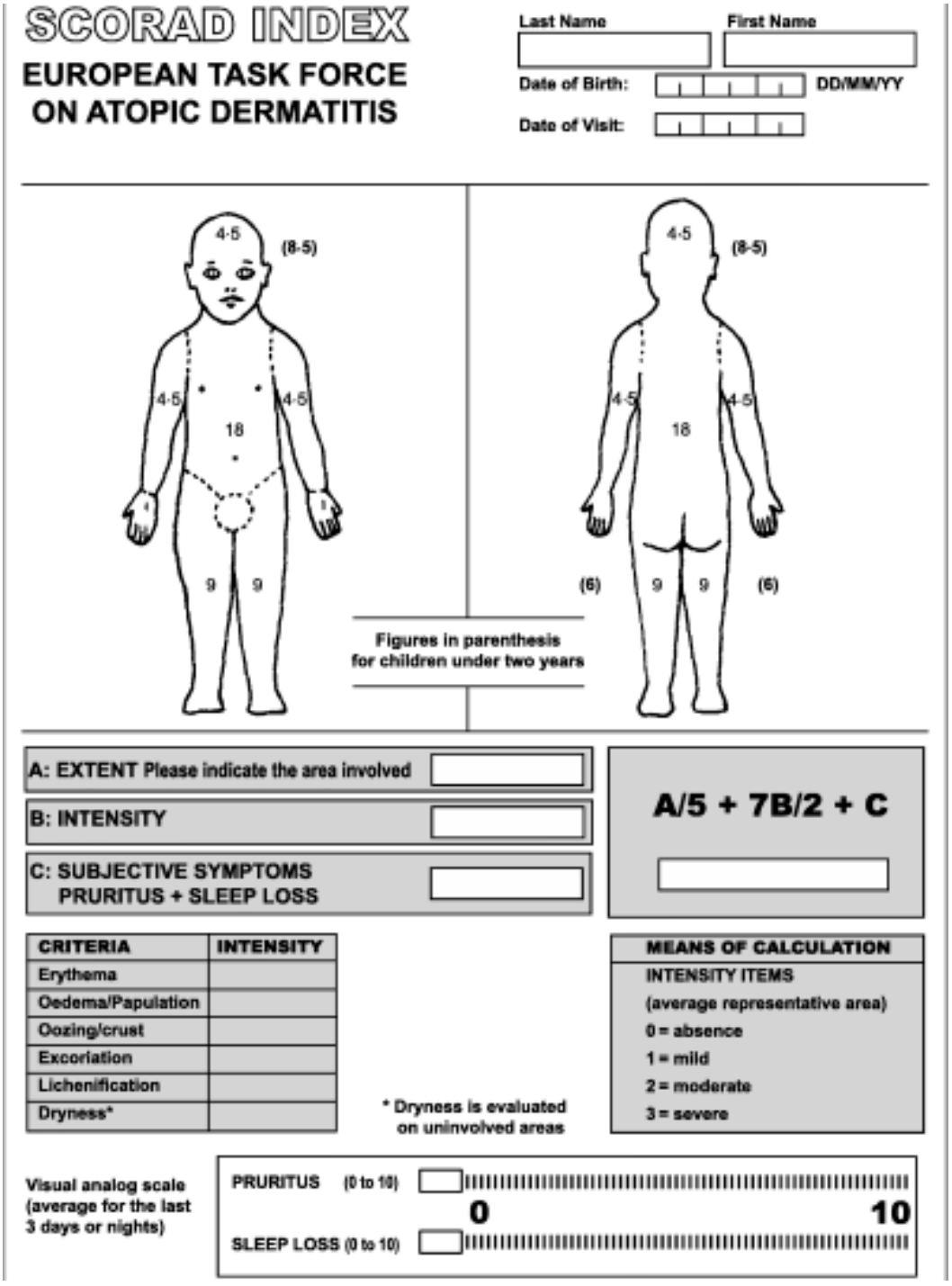

Figure 1. Assessment of disease severity in atopic dermatitis using the SCORAD index

sensitive enough (Mulick et al, 2018; Jaworek et al, 2019). The search for diagnostic markers that will allow the assessment of the allergic inflammatory process and also measure the severity of the disease is ongoing. The backbone of modern mechanisms of development of AD is complemented by the association of the disease with the increased level of eosinophilic cationic protein (ECP; Lee et al, 2011).

During the allergic inflammatory processes,

the release of eosinophils from the bone marrow increases, and their degranulation and ejection of cationic proteins takes place (Karlen et al, 2020). One of the major cationic proteins is the ECP. It is suspected that products of eosinophilic activation are meditators that conciliate late-phase allergic response and are responsible for hyperreactivity in the atopy (Byeon et al, 2020). It has been proven that ECP has a significant proinflammatory effect and plays a role in the development of subacute and chronic signs of allergy and is one of the markers of allergic inflammation (Frazier and Bhardwaj, 2020). However, there is conflicting and limited data on the diagnostic value of ECP in AD (Park et al, 2014).

Aim

Given the difficulty in assessing the activity of the allergic inflammation in patients with AD; especially in severe cases, it is relevant to study the clinical significance of ECP in this pathology. This study aims to analyse the diagnostic significance of ECP in AD patients.

MATERIALS AND METHODS

The methodology of the study was based on the use of a systematic approach to the patients who were assessed at the hospital with complaints that are common for patients with AD.

The inclusion criteria for the study were, a confirmed diagnosis of AD, ≥18 years of age, and a willingness to perform all the procedures that were required by the study design. The diagnosis of AD was established on the basis of criteria formulated by Hanifin and Rajka (1980). All patients were analysed for family and allergic history, objective examination data, and laboratory diagnostic results. The severity scoring of AD, the SCORAD index, was used to assess the severity of exacerbation of the condition *(Figure 1)* (European Task Force, 1993).

All patients with AD were tested for markers of allergic inflammation, namely IgE and erythrocyte sedimentation rate (ESR) in serum (Frazier and Bhardwaj, 2020).

The statistical processing of the results was carried out by the method of variational statistics using the statistical package of Microsoft Office 2010 and Statistica v10 programme.

All procedures performed in the study involving human participants were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Commission of the Ministry of Health of the Ukraine on October 11, 2020, No 13-K6856.

RESULTS

According to the inclusion criteria, 24 patients with AD were examined; 15 patients were female (62.5%). The control group consisted of 10 healthy individuals. In this group, there were 6 women (60%) and 4 men (40%). The patients in the AD group were divided by age: 18–40 years group (7 women and 5 men; average age 31.3±2.1 years old); and >40 years group (8 women and 4 men; average age 56.8±2.6 years old). The mean age of the control group was 41.1±2.3 years old.

Among the patients with AD, urban residents accounted for 63.5% versus 37.5% of people living in the rural. In the study, it was established that people living in urban areas were 2.5 times more likely to suffer from AD compared with those from rural areas ($p<0.01$). The analysis of seasonally exacerbated features of AD showed that 68.8% of patients registered in February–March (i.e. the winter–spring period), and 31.3% were registered in April–May (spring period) ($p<0.05$). In the group of patients with AD, four people were diagnosed with a common form of chronic allergy (16.7%).

The blood pressure of patients with AD was also assessed. The SCORAD index ranged from 18.4 to 78.6 points, averaging 48.5±7.8 points *(Table 1)*.

It should be noted that we did not find a significant difference in the incidence of exogenous and endogenous AD with the criteria of the severity of the disease. Among those examined with a mild course of the disease, the exogenous form of AD was found in two patients (8.3%) and the endogenous form of AD in one patient (4.17%).

We did not find a significant difference in the severity of the disease depending on the age groups. During our study, we analysed the level of total IgE in the patients' serum. A significant difference was found between the mean serum IgE levels, which was 6.2 times higher in AD patients

Table 1. Classification of blood pressure among people with AD (n=24)		
Severity of blood pressure	Number of patients with AD (%)	SCORAD index, points
Mild	3 (12.5%)	16.2 ± 3.8
Moderate	12 (50.0%)	33.5 ± 6.4
Severe	9 (37.5%)	68.6 ± 4.5

(average value: 165.67±5.12 ng/ml), compared with the healthy group (average value: 25.56±5.07 ng/ml; $p<0.05$). It should be pointed out that in the majority of patients with AD (15 people), an increased level of total IgE in serum was detected. However, nine patients with AD had normal values for the level of total IgE in serum.

It should also be noted that concomitant allergic pathologies, mainly allergic rhinitis, conjunctivitis, and bronchial asthma, were found in 7 patients with AD, with an increased level of total IgE in the serum. Taking into account the extrinsic AD and intrinsic AD forms, we used the value of the total IgE level as a basis for isolation of pathogenetic variants of the disease. Notably, along with an increase in the age of patients, there was a tendency towards a decrease in the number of people with an extrinsic form of AD, although the number of people with an intrinsic form of the condition increased. With increased age, there was a decrease in the number of people with the extrinsic form of AD indicated by a high level of IgE, and an increase in the number of people with intrinsic AD indicated by a low level of IgE (odds ratio [OR]: 2.92; 95% confidence interval [CI]: 1.83 to 4.65; p<0.001).

Nevertheless, it must be noted that average level of total IgE in the serum is linkedto the age of the patient (OR: 5.72; 95% CI: 2.52 to 13.94). In the group of patients aged 18–40 years, the average level of total IgE (64.5±3.51 IU/ml) was significantly higher than in the >40 year age group (24.3±4.34 IU/ml; $p<0.05$). In this manner, it can be assumed that with the age, the sensitivity of total IgE is reduced.

We found that the average level of ECP in the serum was 6.5 times higher in patients with AD compared to people without AD. In addition, an elevated serum ECP was detected in the vast majority of AD patients (n=22; 91.7%). All these patients had extrinsic AD (Slobodna et al, 2006). Whereas this indicator did not go beyond the reference values except in 2 (8.3%) people with intrinsic AD.

Furthermore, it was found that as the severity of AD increased, the average serum ECP level also increased (OR: 4.26; 95% CI: 2.01 to 9.05). Among patients with high mean blood serum levels of ECP, the course of the disease was often more severe, namely 4.0 times higher as assessed on the SCORAD index (mean SCORAD index: 54.9±5.4 points), than the moderate level (SCORAD index score: 33.9±5.1 points; $p<0.05$). We did not identify a patient with mild AD and an elevated total serum ECP. Only two patients not exceeding the serum reference ECP levels had a mild disease score (SCORAD index score: 3.9±6.4 points; $p<0.05$).

It is also important to note that the ECP level is positively correlated with the SCORAD score in individuals with both extrinsic AD (r: 0.318; $p=0.002$) and intrinsic AD (r = 0.471; $p=0.002$). In the course of the study, we did not find a significant difference in the value of total serum ECP depending on the age of the patient or the form of the disease. In the course of clinical examination of the patients included in the study, the sensitivity and specificity of the ECP level in AD were determined.

DISCUSSION

Questions remain concerning the aetiology, pathogenesis, and development of AD. According to the literature, eosinophil activation products mediate the formation of an allergic response and are responsible for hyperreactivity in allergies (Park et al, 2014; Kapur et al, 2018). Our study aimed to evaluate the level of ECP as a marker for adult allergic inflammation. In our study we used the total IgE levels as a basis for isolation of pathogenetic variants of the AD. Notably, along with an increase in the age of patients, there was a decrease in the number of patients with an extrinsic form of AD, while the number with the intrinsic form of the disease increased.

In our study, clinical features of intrinsic AD were characterised by a mild degree of severity according to the SCORAD index score and moderately pronounced activity of allergic inflammation, unlike the group of patients with extrinsic AD. On the contrary, the mean value of blood serum ECP in was three times higher in patients with extrinsic AD compared to patients with intrinsic AD. It should be noted that the literature on ECP linkage with the severity by the SCORAD index is controversial and debatable (Byeon et al, 2020). Also, according to the conducted research, in children aged 3–36 months, no correlation was found between both of the studied indicators (Angelova-Fischer et al, 2006). Inversely, some researchers claim that there is a positive correlation between erythrocyte sedimentation rate and SCORAD in AD in both children and adults.

Limitations

The limitations of the study include the small sample size. Further studies are required to confirm our findings. This paper does not investigate the advantages and disadvantages of new approaches for the treatment of AD, including topical and systemic immunosuppressants, as well as biologics and antipruritics.

CONCLUSIONS

Our study has shown in patients with AD, there are pronounced changes in indicators of allergic inflammation, especially ECP. This indicator could serve as a marker of allergic inflammation in AD in adults, depending on the severity of the condition. The level of eosinophilic cationic protein increases alongside the severity of the disease. It does not depend on the age of patients or the pathogenetic form of the disease (extrinsic or intrinsic). In AD, the level of ECP appears to be efficient as an indicator of allergic inflammation. WUK

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