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Atopic and Non-atopic Eczema

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ABSTRACT Atopic dermatitis is a common term used in the medical literature, but according to The Nomenclature Review Committee Of The World Allergy Organization the name which should be used is eczema. Eczema is divided into two subtypes: atopic and non-atopic. These subtypes differ in the level of total immunoglobulin E (IgE) in serum, response to allergens in skin prick tests, and detection of specific IgE antibodies. Non-atopic eczema is characterized by a low level of total IgE, negative skin prick tests, and undetectable specific IgE antibodies. It is estimated that 10-45% cases of eczema are non-atopic ones. In recent studies, other features differentiating these two subtypes have been identified, such as female predominance in non-atopic eczema. A more severe course, damage of the epidermal barrier, predominance of Th2 (T helper cells 2) response, and a lower positive reaction to metal patch tests are the characteristics of the atopic subtype. In our opinion, new diagnostic criteria taking into account the non-atopic subtype of eczema need to be established.

KEY WORDS: atopic dermatitis, atopic eczema, non-atopic eczema

INTRODUCTION

Atopic dermatitis is a chronic and relapsing skin inflammatory disease with characteristic morphology and skin lesions that usually begins during early childhood. The occurrence of atopic dermatitis is estimated at 15-30% in children and 2-10% in adults. During the last 3 decades, the incidence of this disease in developed countries has doubled or even tripled (1).

In order to standardize the diagnosis of atopic dermatitis in the last decades, some diagnostic criteria have been added. In 1980, Hanifin and Rajka introduced a procedure which is based on 4 major and 27 minor criteria. One of the major criteria is the atopic history of the patient and/or family members, whereas a minor criterion indicates increased immunoglobulin E (IgE) serum levels (2). The UK criteria, introduced in 1994, significantly reduced the number of Hanifin and Rajka's criteria and are mainly based on the personal atopic history and clinical features (3). In 1998, the Millennium criteria, which contain the required identification of specific IgE, were presented (4).

The term atopic dermatitis is commonly used in the medical literature despite the fact that The Nomenclature Review Committee Of The World Allergy Organization in 2003 recommended that the name eczema be used instead. Atopic eczema (AE) was identified as an IgE-dependent disease of genetic origin. Its diagnosis is established by skin prick tests or detection of specific IgE from serum (5). AE meets the definition of atopy as a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these patients can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema (5). However, there is a group of patients with similar clinical features as in atopic eczema but with no detectable sensitization to airborne or food allergens and whose total IgE serum level is not increased. The Nomenclature Review Committee of the World Allergy Organization defines it as non-atopic eczema (nAE) (5).

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Various terms for nAE can be found in literature, such as: atopiform dermatitis, non-allergic atopic dermatitis, intrinsic atopic dermatitis, the syndrome of non-allergic atopic eczema/dermatitis, the syndrome associated with T-cell atopic eczema/dermatitis (T-cell associated AEDS) (5-8).

nAE can occur in 10-45% of patients with eczema, and the latest studies point to 27% (9), 37% (10), 12% (6), and 22% (11).

Differences Between nAE and AE

In recent years, many clinical studies related to exploration of the differences between these two subtypes of eczema have been published (6,9-26) (Table 1).

As far as age is concerned, a higher percentage of patients with nAE has been assessed in younger populations with eczema (6,10). Kusel *et al*. found one-third of patients with nAE in a pediatric population with eczema (14). Folster-Holst *et al*. assessed that cases of nAE in adult population were at 6.9% (11). Concerning the sex of eczema patients, female predominance in nAD was widely noticeable (7,11,15,16,26). However, Roguedas-Contios *et al*. pointed out female predominance in both subtypes of eczema (8).

Some studies have indicated a more severe course of the disease in patients with AE on the basis of SCORAD (scoring atopic dermatitis) and stronger itching sensations using VAS (*visual analogue scale)* (15-18). One study, which was based on SCORAD, also found more severe disease in patients with AE. Yet, based on EASI (eczema area and severity index), there was no statistical difference in the disease severity between the groups (6).

Correlations between increased IgE level or elevated levels of Th2 cytokines and escalation of the disease severity (SCORAD) were found in AE. Moreover, a correlation between the severity of skin lesions and elevated levels of Th1 cytokines and IL17 in nAE was discovered (19).

Interestingly, patients with AE used external steroid medications, calcineurin inhibitors, antihistamine drugs, and emollients more frequently. Additionally, their quality of life was estimated as worse than that of the patients with nAE. The relationship between disease severity and the course of disease dependent on stress and environmental factors was less noticeable in patients with nAE (6).

Table 1. Differences between iAD and eAD.

	AD type	
	iAD	eAD
Epidemiology		
• age of the population	younger	elder
• gender predominance	female	no/male
• frequency	10-45%	55-90%
Pathophysiology		
• immune response	Th1	Th2
• infiltration of Th17 and Th 22	high	low
• specific IgE antibodies to food and airborne allergens	-	+
• increased level of IgE receptors on monocytes and dendritic cells	-	+
• level of total IgE	normal	elevated
• skin prick tests to food and airborne allergens	negative	positive
• positive patch tests for metals	frequent	rare
• filaggrin mutations	very rare	frequent
• TEWL (transepidermal water loss)	normal	increase
• skin moisture	sufficient	insufficient
Clinical features		
• atopic family history	rare	frequent
• associated atopic diseases	very rare	frequent
• quality of life	↓	↓↓
• itching	low	high
• non-specific hand or foot eczema	+	+++
• palmar hyperlinearity	+	+++
• keratosis pilaris	+	+++
• pityriasis alba	+	+++
• Dennie-Morgan's fold	++	+
• disease severity	+	++
Treatment		
• use of topical emolients and glucocorticosteroids	rare	frequent
Natural course	iAD ↓ eAD possible	eAD ↓ iAD ?

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Clinical Features

Most researchers agree that both eczema subtypes differ in the frequency of clinical symptoms occurrence. The most frequent symptom in nAE was Dennie-Morgan's fold (38.2% vs 19.7% in AE). The features which predominated in AE were: palmar hyperlinearity (23.8% vs 2.9% in nAE), keratosis pilaris (22.1% vs 5.9%), pityriasis alba (77.9% vs 10.0%), and non-specific hand or foot eczema (31.1% vs 11.8%) (6).

However, different results were obtained by Kulthanana *et al*. in the study performed on a Thai population of 56 patients with eczema (12.5% with nAE), in which ichthyosis vulgaris and non-specific hand and foot eczema occurred more often in patients with nAE. In addition, the influence of environmental factors and stress on the course of the disease was more frequent among patients with nAE (20).

The Skin Barrier

The difference in the skin barrier between the two subtypes of eczema has been indicated as well. Patients with AE are characterized by a defective skin barrier, but nAE patients show no damage to it. TEWL (transepidermal water loss) and skin moisture research showed lower skin moisture and increased TEWL in patients with AE in comparison with healthy patients and those with nAE, who showed no difference (15,21). Furthermore, the loss of filaggrin function predisposes to the development of AE and asthma. Filaggrin mutations are also associated with higher incidences of ichthyosis and palmar hyperlinearity (27). Additionally, disorders of the skin barrier due to decreased or no filaggrin expression as well as enzymatic disorders of the transformation from profilaggrin into filaggrin lead to transdermal penetration of antigens and their increased exposure to the immune system (21,28).

In a Japanese study, the filaggrin gene mutations were observed in 3.7% of the population. The study revealed a significantly higher percentage of filaggrin mutations (8 most frequent mutations in the Japanese population) in patients with AE (9 in 29 patients, 31%) in comparison with nAE ones (1 in 20 patients, 5%) (22). Another study on a group of Japanese patients consisting of 18 subjects with the AE and 19 subjects with nAE reported that the filaggrin mutation was found in 8 patients (44.4%) and 2 patients (10.5%) of each group respectively (16).

The Immune System and Cytokines

Many researchers support the idea that elevated total IgE levels in patients with AE is caused by B lymphocyte activation due to increased concentration of interleukin (IL) 13 and IL4. These interleukins are produced by T helper (Th) 2 lymphocytes located in the skin. Conversely, higher production of INFγ by Th1 lymphocytes can cause suppression of IgE production in patients with nAE (12,16,29,30).

In 2013, Suarez-Farinas *et al*. defined the types of cells in skin lesions of patients with nAE and AE (19). In this study, epidermis hyperplasia was similar in both subtypes. Both subtypes showed intensive inflammatory infiltration and increased levels of T cells and myeloid dendritic cells in comparison with intact skin. Additionally, patients with nAE experienced increased T-cell infiltration of CD3 and CD8, myeloid dendritic cells, Langerhans's cells, and mature dendritic cells in comparison with AE. Less visible differences were found in the amount of inflammatory dendritic epidermal cells, residual dendritic, and atopic dendritic cells. Interestingly, neutrophils were more numerous in the changes of nAE patients while eosinophils and plasmocytic dendritic cells were more numerous in skin lesions of patients with AE.

Greater inflammatory infiltration has been found in patients with nAE. Skin lesions in patients with nAE showed higher or equal infiltration, activity of Th1 and Th2 cells, and much higher infiltration of Th22 and Th17 cells in comparison with AE (19). These differences may indicate the possibility of greater importance of Th22 and Th17 cells in nAE. It has been indicated that the enhanced responses of Th1, Th2, and Th22 in both eczema subtypes, the lack of an immunological shift toward Th2 cells in AE, and proportionally high Th2 activity in nAE mean that the results of this study differ from the findings of previous years. For this reason, it may be assumed that the regulation of IgE secretion is more complex.

The increased level of FOXP3 (forkhead box P3), a marker for regulatory T cells, in skin lesions was found in a patient with nAE (19) whereas these regulatory T cells suppress IgE allergic response and induce immunoglobulin G4 (IgG4) response (31).

Another potential mechanism of reducing IgE levels is the elevated level of IL17A. It causes the inhibition of TSLP (thymic stromal limphopoietin) which is produced by dendritic cells. Inhibition of TSLP secretion reduces Th2 response (32).

Furthermore, cathelicidin production was lower in patients with AE in comparison with nAE (23). This may also be associated with a higher level of IL17 in patients with nAE because IL17 production increases the production of cathelicidin/IL37. The larger number of neutrophils in the tissue may also be associated with the elevated level of Th17 cells/IL17 in patients with nAE.

Higher concentrations of IL4, IL5, IL13 cytokines were found in the peripheral blood of patients with AE, which is typical for Th2 response, whereas nAE patients had a lower concentration of IL4 and IL13 (16,24). Simon *et al*. found that the two eczema subtypes had an increased level of IL-5 and IL13 (33). nAE is characterized by more Th1 lymphocytes in peripheral blood, which causes the increased production of IFNγ and a decrease in the amount of B cells and IgE production (16,34). Patients with AE have lower ability to produce INFγ after stimulation of peripheral lymphocytes by antibody CD3 (34).

It was also confirmed that the number of IgE receptors with high and low affinity (FcεRI and FcεRII/CD23) and α-chain of the IL4 receptor in monocytes significantly increased in patients with AE. IL4 receptors decrease the production of IFNγ by connecting IL4 and IL13. In addition, the polymorphism of IL4R-α (C3223T) and IL4 (C590T) was higher in patients with AE (7). The increase of FcεRI receptor expression in inflammatory dendritic cells in skin lesions of patients with AE was also confirmed. This observation can be considered as one of the diagnostic criteria which differentiate between the two subtypes of eczema (13,35,36).

Sensitivity to Metals

A damaged skin barrier and transepidermal permeation of protein allergens induces a Th2 response, but Th1 cells are induced by non-protein allergens such as metals. The mechanism that causes polarization in the direction of Th1 reaction on haptens of metals is not fully understood. Nickel (Ni) and cobalt (Co) may be presented by the MHC (major histocompatibility complex), and TLR4 (toll-like receptor 4) receptors also react with antigen-presenting cells such as dendritic cells (37,38). High percentage of positive patch tests for metals has been reported in patients with eczema, with no division into subtypes (34). In patients with nAE who have an undamaged skin barrier, there is no protein permeation into the skin and no Th2 response inducement. However, metals can penetrate through undamaged skin which can induce Th1 response.

In a study of 137 children with eczema, 19.3% of patients were positive in metal patch tests (39). The study confirmed that Ni, Co, and chrome (Cr) are the three main metals allergies most frequently detected in the population with eczema (25). The analysis of allergies to Ni, Co, and Cr in 86 patients with eczema gave positive results in 25.6%, 20.9%, and 16.3% patients, respectively. Patients with nAE showed a significantly higher percentage of positive reactions to metals than patient with AE: Ni: 41.9% vs 16.4%; Co: 38.7% vs 10.9%; Cr: 22.6% vs 12.7%, respectively. Generally, positive results to these metals were at 61.3% for nAE (19/31) and 25.5% for AE (14/55). Additionally, higher concentrations of Ni and Co in the sweat were found in patients with nAE. This may indicate that allergy to metals is one of the factors in the development of nAE (37,38).

Possibilities of Transmission Between nAE and AE

In a study of 56 patients initially diagnosed as nAE, 18 of them developed specific IgE in a few years' time (6). Folster-Holst *et al*. noticed a decrease in the number of patients with nAE in an adult population over a period of 7.5 years from 6.8% to 5.4% because of the detection of inhaled allergies (11). By comparing the age of the patients, a higher percentage of patients with nAE was found in the younger population of patients with eczema (10). This may indicate a shift from nAE to AE over time, as can be evidenced from the smaller percentage of patients with nAE in adult populations of eczema patients.

This indicated that the tests for a level of total IgE, specific IgE, and prick tests should be repeated after a period of several years in order to differentiate these two types of eczema if the previous results were negative. Additionally, the tests for specific IgE cannot be sufficiently specific. Patients can be sensitive to inhaled or food allergens which are not examined in routine tests. They can also be allergic to S. aureus antigens, Malassezia sympodialis, or other allergens. Tokura described IgE antibodies against Malassezia sympodialis in patients with AE and nAE, however, according him, those antibodies should not be taken into account in differentiation of eczema subtypes (26).

CONCLUSION

Based on the relevant research, we can confirm that the differences between these two subtypes of eczema are not only in the elevated level of total IgE, specific IgE detection, or positive skin prick tests, but that they are also visible in the clinical picture, skin barrier function, and in the number of inflammatory cells in the skin.

Yet, is this differentiation really needed and will it bring improvement in the patient quality of life? It seems that differences in immunological reactions are the crucial factors which differentiate between these two eczema subtypes. This observation could point to a new way for diagnostic tests and new treatment tactics (e.g. use of IL-17, IL-22 antagonists) as

well as influence detailed prophylactic recommendations. On the other hand, it should be remembered that nAE could transform into AE, and that general prophylactic principles and therapeutic procedures should be identical in both subtypes.

In our opinion, new diagnostic criteria which will take nAE into account should be introduced. In order to resolve disputes on the pathogenesis and differences between these two subtypes of eczema, a study on a large group of patients with standardized diagnostic criteria and testing methods should be conducted.

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