

Original article

Association between the occurrence of the anticardiolipin IgM and mite allergen-specific IgE antibodies in children with extrinsic type of atopic eczema/dermatitis syndrome

Background: As the literature has only controversial data on the role of nonallergen-specific antibodies in atopic eczema dermatitis syndrome, the authors investigated the link between the occurrence of the antiphospholipid [anticardiolipin (ACL), anti- β_2 -glycoprotein I] and allergen-specific immunoglobulin E (IgE) antibodies in 72 children with atopic eczema/dermatitis syndrome (AEDS).

Methods: The measurement of antiphospholipid antibodies was carried out by enzyme-linked immunosorbent assay (ELISA), serum total IgE by nephelometry, and allergen-specific IgE by immunoblotting assay. The statistical analysis was carried out by Fisher's exact test and odds ratio was calculated.

Results: Thirteen of 72 children with AEDS (mean age 8.3 years) had elevated serum levels of ACL, and eight anti- β_2 -glycoprotein I antibodies. The presence of allergen-specific IgE against inhalant allergens and nutritive allergens was among eight of 13 and three of eight in the cases with elevated ACL. The ratio of patients with highly increased severity scoring of atopic dermatitis (SCORAD) index (>75) was significantly higher in the group with elevated (4/13) than in those with the normal ACL levels (2/59). There was a significant association between the appearance of mite (*Dermatophagoides pteronyssinus*, *D. farinae*)-specific IgE and ACL IgM antibodies (6/13).

Conclusion: These findings show that there are significant linkage and association between the appearance of ACL IgM or the production of allergen-specific IgE against inhalant (mainly mite) allergens in children with atopic eczema/dermatitis syndrome.

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Atopic eczema/dermatitis syndrome (AEDS) is a chronic, relapsing, multifactorial skin process with a very complex inflammatory cascade (1–6). Many studies investigated the role of immunologic, physiologic, genetic parameters and the potential provoking factors, e.g. allergens, microbial factors, irritants, seasonal/climate changes and psychic stress in the pathogenesis of the disease (7–11). The impaired skin barrier, sweating function and sweat ion content can also contribute to the induction of AEDS (4, 5, 12, 13). In addition, most of the individuals with AEDS have a personal or family history of allergic rhinitis, conjunctivitis or asthma with increased serum IgE antibodies against inhalant or food allergens (extrinsic, mixed type of AEDS). Some data were presented about the involvement of epithelial and sweat antigens (14, 15). Antinuclear antibodies were observed in an animal model of atopic dermatitis (16) suggesting that antibodies of the nonallergic type also can be present in the sera of patients with AEDS. Ambrozic et al. (17) found that in children younger than 3 years of age (average age: 11 months) the occurrence of antiphospho-

lipid (APL) antibodies was elevated. In this phenomenon they hypothesized the role of nutritive allergens. In this study, we analysed the association of allergen-specific antibodies and two important types of APL, nonallergic [anticardiolipin (ACL), anti- β_2 -glycoprotein I] antibodies in children with AEDS (average age: 8.3 years).

Patients, materials and methods

Thirteen of 72 children investigated (34 boys, 38 girls) with atopic eczema/dermatitis (suffering from serious or medium–severe forms of the disease) were included in the study. Their mean age was 8.3 years (range: 2–15 years). The average of severity scoring of atopic dermatitis (SCORAD) index (17) was 52.3 (range: 32–90). The control group consisted of 22 healthy children (10 boys, 12 girls, mean age 8.6 years). Enzyme-linked immunosorbent assays (ELISA) were used for the measurements of ACL and anti- β_2 -glycoprotein I ($A\beta_2$ -GPI) antibodies. The detection of serum total IgE was carried out by laser nephelometry. The allergen-specific IgE was determined by an immunoblot assay (INTEX, Basel, Switzerland). Statistical analysis was performed by Fisher's exact test and odds ratio was calculated.

Results

Linkage between the increased anticardiolipin and anti- β 2 glycoprotein I antibodies and the amounts of serum total IgE, allergen-specific IgE in patients with AEDS

The number of patients with elevated levels of antiphospholipid antibodies was significantly higher (18/72, 25%) than in the normal controls (1/22), $P = 0.0378$ the odds ratio being 7. The distribution of the various isotypes of antiphospholipid antibodies was found as follows, ACL IgM 12, IgG in two, A β 2-GPI IgM in six, and IgG in three of the 18 patients. In the 13 patients with ACL positivity (11 of IgM, one of IgG and IgM, one of IgG type) the elevated level of serum total IgE was remarkable, i.e. in eight of 13 patients, whereas six of eight also presented specific IgE positivity. However, only two of 13 patients with high level of anticardiolipin antibodies showed IgE positivity with normal levels of serum total IgE. In the eight subjects with specific IgE positivity, the distribution of allergens reacting with allergen-specific IgE was as follows: in five cases inhalant allergens alone, in three cases inhalant plus food allergens (Table 1).

The types of allergens in the patients with AEDS

If we analysed the association of ACL and allergen-specific IgE antibodies, it was surprising that mite (*Dermatophagoides pteronyssinus*, *D. farinae*)-specific IgE positivities occurred in six of the 13 patients vs 10 of 59 patients in the group with normal levels of ACL antibodies, with an odds ratio of 4.2, and $P = 0.0322$. This tendency was not statistically significant and the occurrence of weed-specific IgE (5/13 vs 11/59, odds ratio 2.7) represented the second place, and the rye-specific IgE (6/13 vs 18/59, odds ratio 1.95) represented the third place

in the frequency of allergen-specific antibodies. All these three allergens are of inhalant type (Table 2).

Comparison of SCORAD index and the occurrence of anticardiolipin antibodies in children with extrinsic type of AEDS

The occurrence of most severe form (SCORAD > 75) of AEDS was significantly higher in the group of patients with high ACL level (4/13) than in patients with normal levels of ACL (2/59), odds ratio 9.077, $P = 0.0185$. There was no association between the high values of the SCORAD index and allergen-specific IgE positivity.

Discussion

In the pathogenesis of AEDS, the genetically inherited damage of skin can play a crucial role (4, 5, 9, 10, 13, 19, 20). The impaired skin barrier functions, namely, disorder of sweating, ceramide metabolism, high-affinity IgE receptors, and the fibrinogen and fibronectin binding capacity can be important factors not only in the skin colonization with *Staphylococcus aureus* but also in the unusual, skin-mediated polysensitization by various allergens, normally neutral and unpenetrable for the organisms. According to these data, there was a strong association between the appearance of ACL IgM and mite-specific IgE antibodies in children with extrinsic type of AEDS (average age 8.3 years). The SCORAD index (18) reflecting the severity of AEDS was also the highest in the patients with high levels of ACL positivity. According to these data the increased appearance of ACL antibodies can be observed also in children with AEDS older than 3 years (17, 21–23).

Table 1. Linkage between the increased anticardiolipin and anti- β 2 glycoprotein I antibodies and the amounts of serum total IgE, allergen-specific IgE in patients with AEDS

Patients	Anticardiolipin IgM and IgG (normal: IgG < 22, IgM < 16 U/ml)	Anti- β 2 glycoprotein I IgM and IgG (normal: IgG < 14.6, IgM < 34 U/ml)	Serum total IgE (normal: 100 < U/ml)	IgE positivity
1	IgM: 21.9		78.7	Inhalant
2	IgM: 22.5		3234.0	Inhalant + food
3	IgM: 44.8		142.1	—
4	IgM: 34.1		2388.0	Inhalant
5	IgM: 33.2		212.6	Inhalant
6	IgM: 28.9		54.9	—
7	IgM: 21.1		819.6	Inhalant
8	IgM: 118.5			
	IgG: 36.3		17.5	—
9	IgG: 25.4	IgM: 45.3	17.5	Inhalant + food
		IgG: 32.3		
10	IgM: 24.3	IgM: 37.2	268.4	Inhalant
11	IgM: 29.4	IgM: 121.7	225.7	—
12	IgM: 18.9		525.6	Inhalant + food
13	IgM: 25.9		17.5	—
Ratio of positivity	13/13	3/13	8/13	8/13

Figures and letters in bold reflect pathologic data.

Table 2. The types of allergens in the patients with AEDS ($n = 72$)

Allergens	Patients with high levels of anticardiolipin antibody (13/72 = 18%)	Patients with normal levels of anticardiolipin antibody (59/72 = 82%)	P-value	Odds ratio
Rye spec. IgE	6	18	ns	1.95
Mite spec. IgE	6*	10	$\leq 0.0322^*$	4.2
Weed spec. IgE	5	11	ns	2.7
Grasses	2	12	ns	0.72
Cat and/or dog	2	12	ns	0.72
Trees	2	6	ns	1.6
Corn	2	4	ns	2.5
Soy	2	4	ns	2.5
Tomato	2	3	ns	3.39
Any type of allergen spec. IgE	8	29	ns	1.65
Total number of allergen spec. IgE positivity	8/35	29/93	ns	1.708

* Statistically significant difference.

However, in this group of children the association of APL antibodies exists to the inhalative and not to the nutritive allergens (17, 23). We do not think that these ACL IgM antibodies may have a dominant role in the pathogenesis and maintenance of the disease (23). However, we do suppose that the appearance of these APL antibodies can be related to the presence of various inhalant allergens, mainly of mite, weeds and rye in the children with extrinsic type AEDS. These allergens can induce allergen-specific IgE antibody production, whereas some lipid components of these allergens, e.g. inositol-phosphatides occurring both in animal and plant tissues, simultaneously provoke antibodies of the APL type also. This situation can be similar to that when lipids of microorganisms initiate the production of ACL IgM during infections (24). The increased appearance of APL antibodies, however, cannot be the part of a generalized polyclonal antibody production of AEDS patients with atopic character, presenting elevated total serum IgE levels, as the very severe form of disease (cases with SCORAD index higher than 75) occurred independently from the levels of allergen-specific or total serum IgE. Therefore, in the association of the increased ACL IgM and mite and other inhalant allergen-specific IgE production (25–27), we think the unusual, possibly skin-mediated uptake of allergens (20) to play the initiating role. The lipid components of these allergens can be the triggers for the production of antibodies of the APL type. It has to

be mentioned, however, that we earlier found the more frequent appearance of antiphospholipid and antinuclear antibodies in children with AEDS showing normal levels of serum total IgE than in those with high levels of serum total IgE (extrinsic type of AEDS) (23). It is the point in the present study that in those fewer number of patients who have APL antibodies in spite of their extrinsic type of AEDS, the association of these antibodies occurred mainly with mite- and other inhalant allergen-specific IgE antibodies. Both types of antibodies can be regarded as consequences of the damaged skin barrier function in patients with AEDS. In the most severe form of AEDS (with SCORAD index higher than 75) the APL antibody positivity could be a secondary marker of the disease activity. However, APL antibodies may not have any significant and specific pathogenic or diagnostic value in the disease.

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