

Food allergy, asthma bronchiale, and rhinitis in atopic dermatitis patients with total immunoglobulin E under and above 200 IU/ml

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The objective of this study is to evaluate if there is a difference in the occurrence of asthma bronchiale, rhinitis, pollen allergy, food allergy and sensitization to basic food allergens, onset of atopic dermatitis (AD), family history about atopy, and duration of eczematous lesions in AD patients with the level of total immunoglobulin E (IgE) under or above 200 IU/ml. Complete allergological and dermatological examination was performed and the statistical evaluation of the relations among the patients with the level of IgE under 200 IU/ml and above 200 IU/ml was performed. Out of 277 patients suffering from AD, we included 87 men and 190 women; the average age was 25.9 years. From 277 patients, 92 patients (33%) have IgE under 200 IU/ml; in these patients, the occurrence of tested parameters is significantly lower in comparison to patients with IgE above 200 IU/ml.

Keywords: atopic dermatitis; total IgE; food allergy; asthma bronchiale; pollen allergy; onset of atopic dermatitis

Introduction

Atopic dermatitis (AD), allergic rhinitis, and asthma bronchiale are atopic diseases that develop on a complex of genetic background, the so-called atopic diathesis; although they target different organs, in most patients they are characterized by the presence of elevated total serum immunoglobulin E (IgE) levels (Beasley, Crane, Lai, & Pearce, 2000; Burrows, Martinez, Halonen, Barbee, & Cline, 1989; Ishizaka & Ishizaka, 1967; Sunyer et al., 1995). The theory describing atopic diseases as highly IgE-dependent has persisted over a long time; however, a subgroup of atopic patients exhibits normal IgE levels and mechanisms contributing to the so-called “intrinsic” or “nonallergic form” have been the matter of intensive research work in the last years and new data have raised the question of the precise role of IgE in atopy. Generally, atopic diseases can be divided into two distinct variants: the extrinsic, allergic variant, which occurs in the context of sensitization toward environmental allergens and is accompanied by elevated serum IgE levels, and the intrinsic, nonallergic variant, with no detectable sensitization and with low serum IgE levels (Wüthrich, 1989). But, according to the latest studies, there is no consensus regarding the definitions of intrinsic AD; it has become increasingly clear that allergic and nonallergic forms exhibit specific clinical and immunologic characteristics

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(Schmid-Grendelmeier, Simon, Simon, Akdis, & Wuthrich, 2001). According to some studies (Bos, Van Leent, & Sillevius, 1998; Wüthrich, 1983, 1989, 1999), AD patients with intrinsic form suffer from a “pure” type of AD, it means, without previous or current associated respiratory diseases. These patients show normal total serum IgE levels, no specific IgE (sIgE), and negative skin prick tests (SPTs) to environmental or food allergens. Some authors think that a strict distinction of intrinsic and extrinsic variant is impossible because intrinsic AD may develop into extrinsic over time (Roguedas-Contios & Misery, 2011). The hypothesis of a dynamic relationship between the two forms of AD is supported by the data in a study investigating the persistence of AD during the development of respiratory allergic diseases (Novembre et al., 2001). The level of total IgE is one of the main factors determining the variant of AD. At present, it has not been evaluated whether AD patients with normal level of IgE, in contrast to patients with higher level of total IgE, have a higher risk of an allergic rhinitis or developing allergic asthma, as well as food allergy. In addition, nor has the frequency been evaluated of concomitant nonallergic rhinitis and/or nonallergic asthma in the nonallergic subgroup of AD (Novak & Bieber, 2003). The aim of our study is to evaluate if there is a difference in the occurrence of asthma bronchiale, rhinitis, duration of AD lesions (persistent or occasionally), food allergy, and sensitization (basic food allergens such as cow milk, wheat, peanut, soy, and egg), the positive family history of atopy, pollen allergy and the onset of AD in patients with the level of total IgE under 200 IU/ml and above 200 IU/ml.

All patients included signed the informed consent with the study and agreement of local Ethics committee was given to this study.

Method

In the period from January 2005 to November 2013, we included 277 patients suffering from AD at the age 14 of years or older. The diagnosis of AD was made with the Hanifin-Rajka criteria (Hanifin & Rajka, 1980). Complete dermatological and allergological examination was performed at the Department of Dermatology and Venereology, Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic. The following parameters were examined: total IgE, asthma bronchiale, rhinitis, duration of AD, family history of atopy, pollen allergy, food allergy and sensitization, and onset of AD. The statistical evaluation of the relations among individual parameters was performed; we asked, if there was a significant relationship between the patients with the level of total IgE under/above 200 IU/ml and the occurrence of asthma bronchiale, rhinitis, duration of AD lesions (persistent or occasionally), positive family history about atopy, pollen allergy, and onset of AD.

Evaluation of parameters we monitored

The serum level of total IgE

It has been measured with the method of Fluorescent Enzyme ImmunoAssay (FEIA) (Pharmacia CAP system, Uppsala, Sweden). The level of total IgE higher than 200 IU/ml was assessed as positive.

The diagnosis of asthma bronchiale

It was made according to the results in spirometry at allergological outpatient department.

The evaluation of rhinitis (seasonal or perennial)

It was made according to the anamnestical data.

The evaluation of duration of AD

The AD lesions were evaluated as persistent or occasionally, according to the dermatologist examination during one previous year and according to the patient information.

The onset of AD

It was evaluated according to the patient history (the onset of AD below 5 years of age or later).

The family history

The atopy history evaluated according to the patient information (the occurrence of allergy, AD, asthma bronchiale, rhinoconjunctivitis in parents, brothers, sisters, and children).

The evaluation of pollen allergy

The occurrence of pollen allergy was determined according to the history of the pollen allergy to grass and trees (grass as Poaceae family *Poa pratensis*, *Phleum pratense*, *Dactylis glomerata*, and *Cynodon dactylon*, and birch) and according to the sIgE level and the SPT results for pollen (containing Bet v 1 and Bet v 2 allergens and for pollen containing homologous allergens). Commercial extracts Alyostal (Stallergens, France) was used for SPTs. The serum level of the sIgE has been measured with the method of CAP (system FEIA – Pharmacia Diagnostics, Uppsala, Sweden). The level of sIgE higher than 0.35 U/ml was assessed as positive. Allergy to pollen was defined as having a clear history of allergic reaction to pollen with the positive results in SPTs or sIgE (Celakovska & Bukac, 2014).

The diagnosis of food allergy

Allergy to cow milk, wheat flour, egg, peanuts, and soy was made according to the results in sIgE, SPT, atopy patch test (APT), and the open exposure tests. Patients with a positive result in the open exposure test (early and/or late reactions) with examined food and with a positive result in at least one of the diagnostic method (sIgE, APT, SPT) to this food were regarded as the patients with food allergy. Patients with an early reaction after the ingestion of examined food repeatedly in their history from their childhood were also classified as patients with food allergy; the open exposure test was not performed in these patients because of anaphylactic reaction danger (Celakovska & Bukac, 2014; Celakovska, Ettlerova, Ettler, Vaneckova, & Bukac, 2011, 2015a, b).

Sensitization to food allergens (cow milk, wheat flour, egg, peanut, and soy)

It was confirmed in patients with positive results in sIgE and/or SPT and/or APT, but not with negative results in the open exposure test to the food allergens (Celakovska & Bukac, 2014; Celakovska et al., 2011, 2015a, b).

Statistical analysis

We evaluated if there was a significant difference in the occurrence of asthma bronchiale, rhinitis, duration of AD lesions (persistent or occasionally), the positive family history

about atopy, pollen allergy, food allergy, sensitization to food allergens, and the onset of AD in patients with the level of total IgE under 200 IU/ml and above 200 IU/ml.

Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Results

In total, 277 patients suffering from AD were included in the study: 87 men and 190 women entered the study with the average age of 25.9 years (s.d. = 9.2 years), minimum age = 14 years, maximum age = 63 years.

The results of the occurrence of follow-up categories and their statistical analysis are summarized in 11 tables.

Table 1 indicates the occurrence of the parameters observed in patients with AD. Out of 277 patients, 120 (43%) suffer from asthma bronchiale, 202 (73%) patients suffer from rhinitis, persistent lesions of AD in one previous year were recorded in 175 (62%) patients, and only occasional lesions were recorded in 102 (38%) patients. Positive findings about atopy in family history were recorded in 162 (58%) patients; no data about atopy in family history were recorded in 115 (42%) patients. The onset of AD below 5 years of age was recorded in 214 (77%) patients; later onset of AD was recorded in 63 (23%) patients. Pollen allergy occurred in 129 (47%) patients. Number of patients with food allergy to examined food allergens was 78 (28%) and number of patients with food sensitization was 146 (53%). Number of patients with the level of IgE under 200 IU/ml was 92 (33%) and number of patients with the level of IgE above 200 IU/ml was 185 (67%). Number of patients without rhinitis and asthma bronchiale (= pure form of AD) was 68 (24%). Number of patients with mixed form was 209 (76%) patients.

Tables 2–11 indicate the occurrence of patients with the IgE under and above 200 IU/ml and the occurrence of following parameters.

Table 1. Occurrence of monitored parameters in 277 patients with AD.

Monitored parameter	Number of patients (%) of 277	
Asthma bronchiale	120 (43%) yes	157 (57%) no
Rhinitis	202 (73%) yes	75 (27%) no
AD – the duration of lesion in one year	Occasional 102 (38%)	Persistent 175 (62%)
Family atopy history	162 (58%) positive	115 (42%) negative
Onset of AD	Under 5 years of age: 214 (77%)	Later than in 5 years of age: 63 (23%)
Pollen allergy	129 (47%) yes	148 (53%) no
Food allergy (cow milk, wheat, peanuts, soy, egg)	78 (28%) yes	199 (72%) no
Sensitization to food (cow milk, wheat, peanuts, soy, egg)	146 (53%) yes	131 (47%) no
Respiratory allergies (asthma bronchiale and/or rhinitis)	209 (76%) yes	68 (24%) no
Total IgE	Under 200 IU/ml 92 patients (33%)	Above 200 IU/ml 185 patients (67%)

Table 2. The classification of patients according to the occurrence of asthma bronchiale and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Asthma bronchiale	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
Asthma bronchiale +	24 (9%)	96 (35%)	120 (43%)
Asthma bronchiale –	68 (24%)	89 (32%)	157 (57%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value	0.0000 *		

*The dependence is significant.

Asthma bronchiale

Of 120 patients suffering from asthma bronchiale, 24 patients have IgE under 200 IU/ml and 96 above 200 IU/ml; of 157 patients without asthma bronchiale, 68 have IgE under and 89 above 200 IU/ml. The dependence is significant (Table 2).

Sex

Of 87 males, 64 have IgE above and 23 under 200 IU/ml; of 190 females, 69 have IgE under and 121 above 200 IU/ml. There is no significant dependence (Table 3).

Rhinitis

Out of 202 patients suffering from rhinitis, 46 patients have IgE under and 156 above 200 IU/ml. Of 75 patients without rhinitis, 46 have IgE under and 29 above 200 IU/ml. The dependence is significant (Table 4).

History

Of 162 patients with positive data in their atopy history, 41 patients have IgE under and 121 above 200 IU/ml. Of 115 patients with no history about atopy, 51 have IgE under and 64 above 200 IU/ml. The dependence is significant (Table 5).

Table 3. The classification of patients according to sex and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Sex	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
Males	23 (8%)	64 (23%)	87 (31%)
Females	69 (25%)	121 (44%)	190 (69%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value	0.105		

Table 4. The classification of patients according to the occurrence of rhinitis and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Rhinitis	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
Rhinitis +	46 (17%)	156 (56%)	202 (73%)
Rhinitis –	46 (17%)	29 (10%)	75 (27%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value	0.0000 *		

*The dependence is significant.

Food allergy

Of 78 patients suffering from food allergy, 12 patients have IgE under and 66 above 200 IU/ml. Of 199 patients with no food allergy, 80 have IgE under and 119 above 200 IU/ml. The dependence is significant (Table 6).

Sensitization to examined foods

Of 146 patients with sensitization to examined foods, 36 have IgE under and 110 above 200 IU/ml, of 131 patients with no sensitisation, 56 have IgE under and 75 above 200 IU/ml. The dependence is significant (Table 7).

Pollen allergy

Of 129 patients suffering from pollen allergy, 25 patients have IgE under and 104 above 200 IU/ml, of 148 patients without pollen allergy, 67 have IgE under and 81 above 200 IU/ml. The dependence is significant (Table 8).

Duration of lesions

Of 175 patients suffering from persistent lesions, 33 have IgE under and 142 above 200 IU/ml; of 102 patients with occasional lesions, 59 have IgE under and 43 above 200 IU/ml. The dependence is significant (Table 9).

Table 5. The classification of patients according to the occurrence family history and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

History	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
History +	41 (15%)	121 (44%)	162 (59%)
History –	51 (18%)	64 (23%)	115 (41%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value	0.001*		

*The dependence is significant.

Table 6. The classification of patients according to the occurrence of food allergy and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Food allergy (cow milk, wheat, peanuts, soy, egg)	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
Food allergy +	12 (4%)	66 (24%)	78 (28%)
Food allergy –	80 (29%)	119 (43%)	199 (72%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value		0.000 *	

*The dependence is significant.

Onset of AD

Of 214 patients with the onset of AD below 5 years of age, 58 have IgE under and 156 above 200 IU/ml; of 63 patients with the onset above 5 years of age, 34 have IgE under and 29 above 200 IU/ml. The dependence is significant (Table 10).

Respiratory diseases (asthma bronchiale and/or rhinitis)

Of 209 patients suffering from respiratory diseases (asthma bronchiale and/or rhinitis), 49 patients have IgE under 200 IU/ml and 160 have IgE above 200 IU/ml. Of 68 patients without respiratory diseases, 43 have IgE under 200 IU/ml and 25 patients above 200 IU/ml. The dependence is significant (Table 11). Of 43 patients (15%) with IgE under 200 IU/ml, 20 patients (7%) are without sensitization against food and inhalant allergens and 23 (8%) patients suffer from sensitization to some of the examined allergens.

Discussion

In our study, the comparison in the occurrence of asthma bronchiale, rhinitis, pollen allergy, history, sex, food allergy and sensitization to basic food allergens, onset of AD, and the duration of lesions was performed according to the level of total IgE. In patients

Table 7. The classification of patients according to the sensitization and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Sensitization (cow milk, wheat, peanuts, soy, egg)	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
Sensitization +	36 (13%)	110 (40%)	146 (53%)
Sensitization –	56 (20%)	75 (27%)	131 (47%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value		0.002 *	

*The dependence is significant.

Table 8. The classification of patients according to the occurrence of pollen allergy and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Pollen allergy	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
Pollen allergy +	25 (9%)	104 (37%)	129 (46%)
Pollen allergy –	67 (24%)	81 (30%)	148 (54%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value	0.0000 *		

*The dependence is significant.

with IgE lower than 200 IU/ml (92 patients, 33%), the occurrence of asthma bronchiale, rhinitis, history about atopy, pollen allergy, the occurrence of persistent lesions, the sensitization to food allergens and food allergy to basic food allergens is significantly lower in comparison to patients with IgE above 200 IU/ml (67%). No significant relationship was found between sex and the level of total IgE.

According to some authors, it may be important to separate the intrinsic (nonallergic) and extrinsic (allergic) forms of AD because their pathophysiologies appear to be inherently different (Roguedas-Contios & Misery, 2011). Elevated total IgE is frequently included as a diagnostic criterion for allergic diseases. At present, it has not been evaluated whether patients with allergic AD, in contrast to patients with nonallergic AD, have a higher risk of allergic rhinitis or risk of developing an allergic asthma, as well as food allergy. In addition, the frequency of concomitant nonallergic rhinitis and/or nonallergic asthma in the nonallergic subgroup of AD patients has not been evaluated (Novak & Bieber, 2003). Novak considered patients with intrinsic AD to have low or moderate total serum IgE levels (<150 kU/l) in combination with negative in vitro IgE screening for airborne allergens and food allergens (e.g., CAP-RAST), as well as negative prick test results for standard airborne allergens and food allergen and the absence of other atopic diseases (Novak & Bieber, 2003). A cut-off of total serum IgE level of 150kU/l was selected to distinguish extrinsic and intrinsic types of AD in the study of Roguedas-Contios and Misery (2011). Mori classified patients with total serum IgE levels <220/ml as opposed to having intrinsic AD and those with levels >400/ml⁻¹ as having extrinsic AD (Mori et al., 2010). Despite the lack of a

Table 9. The classification of patients according to the occurrence of persistent or occasional lesions and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Duration of lesions	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
Persistent	33 (12%)	142 (51%)	175 (63%)
Occasional	59 (21%)	43 (15%)	102 (36%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value	0.0000 *		

*The dependence is significant.

Table 10. The classification of patients according to the onset of AD and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

AD under/above 5 years of age	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
AD under 5 y	58 (21%)	156 (56%)	214 (77%)
AD above 5 y	34 (12%)	29 (10%)	63 (22%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value		0.000 *	

*The dependence is significant.

universal consensus, Ott et al. (2009) have shown that total serum levels can be regarded as a clinically useful parameter, as can the presence of allergen-specific Ig antibodies.

The cut-off of the total serum IgE level of 200 IU/ml is recommended at our study to distinguish allergic and nonallergic variant of AD. Out of 92 patients (33%) with IgE under 200 IU/ml, 49 patients (18%) suffer from respiratory diseases (asthma bronchiale, rhinitis) and 43 patients (15%) suffer from AD without respiratory diseases; of these patients, only 20 patients (7%) are without sensitization against food and inhalant allergens. Generally, the frequency of patients suffering from intrinsic AD is quite variable, ranging from 16% (Somos & Schneider, 1993) to over 25% in East German schoolchildren (Schäfer, Dockery, Kramer, Behrendt, & Ring, 1997; Schäfer et al., 1999), and up to 45% in a French study of children, the latter based on skin tests only (Cabon, Ducombs, Mortureux, Perromat, & Taieb, 1996). In other studies they observed a frequency of intrinsic AD of up to 40% of all AD patients (Schmid-Grendelmeier et al., 2001). Patients with intrinsic AD tend to have a late onset of the disease but otherwise family history and disease duration seem to be similar in intrinsic AD and extrinsic AD (Werfel & Kapp, 1999). In the study done by Fölster-Holst, Pape, Buss, Christophers, and Weichenthal (2006), the intrinsic form of AD was defined by low total serum IgE serum levels (<200 kU/l), the absence of associated respiratory diseases and a lack of allergen-

Table 11. The classification of patients according to the occurrence of respiratory diseases (asthma bronchiale and/or rhinitis) and the level of total IgE. Pairs of these categories were entered in contingency tables and the chi-square test of independence of these classifications was performed with the level of significance set to 5%.

Respiratory disease (asthma bronchiale and/or rhinitis)	Number of patients		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Total
Respiratory disease +	49 (18%)	160 (58%)	209 (75%)
Respiratory disease –	43 (15%)	25 (9%)	68 (25%)
Total	92 (33%)	185 (67%)	277 (100%)
<i>p</i> -value		0.0000 *	

*The dependence is significant.

specific serum IgE antibodies and negative SPT for common allergens. In our study, 20 patients (7%) could be considered patients with intrinsic form of AD – the total IgE is under 200 IU/ml, they have no respiratory diseases and no sensitization to basic food and aeroallergens; this frequency of intrinsic form of AD is the same as in the study of Fölster-Holst et al. (2006).

Conclusion

Total IgE under 200 IU/ml was recorded in 33% of patients suffering from AD. In these patients, the occurrence of asthma bronchiale, rhinitis, history about atopy, pollen allergy, the occurrence of persistent lesions, the sensitization to food allergens and food allergy to basic food allergens is significantly lower in comparison with patients with IgE above 200 IU/ml. In 7% of patients suffering from AD, no sensitization to food and inhalant allergens was recorded.

Disclosure statement

No potential conflict of interest was reported by the authors.

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