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Are Respiratory Allergic Diseases Related to Atopic Dermatitis?

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A B S T R A C T

The difference of test results between patients with »pure« atopic dermatitis (AD) and »mixed« AD (with concomitant respiratory allergy, RA) was investigated in 30 AD patients. The results showed the onset of disease that mostly occur in the early infancy [15 (50%) patients had developed the disease under the age of 2 – 2/10 in »pure« AD, and 13/20 in »mixed« AD]. Twenty (66.6%) of them had a history of RA (»mixed« AD) whereas the remaining 10 (33.3%) had »pure« AD. Seventeen (56.6%) AD patients had one concomitant allergic disease, while 3 (10%) patients had two comorhid conditions (AR and AB) each. Family history was positive for atopy in 22 (73.3%) AD patients [in 14 (46.6%) patients in a first-degree relative]. Twenty-four (80%) patients had positive prick test [9/10 (90%) in »pure« AD and 15/20 (75%) in »mixed« AD], mostly for house dust (20). Positive scratch test was observed in 16 (53.3%) patients [4/10 in »pure« AD, and 12/20 in »mixed« AD]. Nineteen (63.3%) AD patients showed positive patch test reaction [5/10 in »pure« AD, and 14/20 in »mixed« AD]. AD patients had higher serum IgE (21/30) than non-atopic ones but similar in »pure« AD, and »mixed« AD [7/10 (70%) in »pure« AD, and 14/20 (70%) in »mixed« AD]. Determination of CD23 marker on B-lymphocytes showed normal values in 24, and increased values in six patients [2/10 in »pure« AD, and 4/20 in »mixed« AD]. The values of CD21 were decreased in 16 AD patients [6/10 in »pure« AD, and 10/20 in »mixed« AD]. HLA-DR expression was normal in almost all patients. There were no statistically significant differences ($p<0.05$) between the »pure« AD and »mixed« AD patient groups, except for the age at onset, which was younger in the group of patients with concomitant RA. Accordingly, study results pointed to the association between AD and RA.

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Introduction

Previous studies have demonstrated similar mechanisms to be involved in the pathogenesis of atopic diseases, e.g., allergic bronchial asthma (AB), allergic rhinoconjunctivitis (AR), and atopic dermatitis (AD)[1–5].

The difficulties with the use of the term atopic disease rest in the fact that they are associated with IgE-mediated allergic reactions of the immediate type (type I of Coombs and Gell), whereas in AD there is a combined action of several immunologic and nonimmunologic factors[1]. There is an increasing evidence that the activation of T helper cells producing Th2-related cytokines with IL-4, IL-5 and IL-6 but not IL-2 and interferon-gamma (IFN-gamma) may be involved in their pathogenesis[6].

Atopic dermatitis usually manifests in the early infancy. The concomitant symptoms of respiratory allergies (RA) occur in 30%–50% of AD patients and usually develop after the childhood phase of AD[1–3]. In general, the severity of AD decreases after the first year of life, skin lesions are milder and not infrequently disappear completely by around the age of 30 (Figures 1 and 2). The relationship of AD with other atopic manifestations such as AB or AR has not yet been definitely demonstrated. Because of the similarity of these diseases, there is a proposal to distinguish three main subtypes of AD: »mixed« type with concomitant RA, »extrinsic« type of »pure« AD without RA but with allergen-specific IgE, and »intrinsic« type without immediate type sensitizations[7].

The sensitization of the immediate type is demonstrated by an immediate urticarial reaction to the allergens in skin tests (prick, scratch and intracutaneous test), and occasionally positive skin tests of delayed hypersensitivity (patch test). Even in the early childhood, skin tests show that these patients exhibit positive reactions of the immediate type to food and inhalant allergens. Skin tests and determination of increased IgE values are common diagnostic parameters, however, recent flow cytometry studies of cell markers on B-lymphocytes (e.g., CD21 and CD23) and T-lymphocytes (e.g., HLA-DR) may contribute to the understanding of the pathogenesis of AD.

The aim of our study was to examine by different test parameters the allergologic status in AD patients and to define whether AD patients with concomitant RA (»mixed« AD) had more prominent allergologic status and more positive tests than those without RA (»pure« AD), thus being at a higher risk of RA.

Subjects and Methods

Subjects

Thirty patients with AD (16 females and 14 males, aged 4–44 years) and 10 healthy controls (a group of subjects in whom atopy was definitely excluded; 6 females and 4 males, aged 5–63 years) participated in the clinical study. None of the subjects had acute infections. AD patients had typical clinical signs of AD. The criteria for the diagnosis of AD were those given by Hanifin & Rajka[3]. None of the patients had received any treatment for at least one week before the study and none had taken oral steroids.

Study protocol

Data on the skin and respiratory diseases were obtained from personal and family histories. The subjects were asked to complete a questionnaire on allergic respiratory disorders, and were clinically examined. Consultations were performed by a dermatologist, and history data on allergic disorders were reviewed and discussed with each subject. Information was obtained on the past and/or current symptoms of AD, allergic rhinoconjun-

ctivitis (AR), allergic bronchitis/asthma (AB), and family history of allergic diseases. The severity of AD was determined according to the criteria defined elsewhere[8].

The aim was to define whether AD patients with concomitant RA (»mixed« AD) had more prominent allergologic status and more positive tests than those without RA (»pure« AD), thus being at a greater risk for the development of RA.

Methods

Skin prick tests to a standard series of inhalant and nutritive allergens and scratch test to preservatives and additives were performed using commercial solutions (supplied by the Institute of Immunology, Zagreb). Negative (50% mix of glycerin and saline) reaction and positive (histamine) controls were included. The tests were performed on clinically uninvolved skin on the subjects' forearms. The wheal diameter was measured at 20 minutes, and a diameter of > 3 mm was taken as positive[9]. The result was considered positive if at least one allergen of the standard test series was positive.

The epicutaneous (patch) test was carried out with the standard series allergens according to the International Contact Dermatitis Research Group (ICDRG) in adult patients with AD and in children aged > 5[9–11]. Patch test results with one or more plus (+) to particular contact allergens were considered positive according to ICDRG.

The values of total IgE were determined by the standardized radioimmunosorbent test (Pharmacia, Uppsala, Sweden) and enzyme-linked immunosorbent assay (ELISA)[9,11]. The upper limit normal for IgE values was 150 IU/mL in adults, and was age-adjusted in children[11,12]. The expression of CD21 and CD23 markers on B-lymphocytes and of HLA-DR on T-lymphocytes was determined in peripheral blood (three-color immunofluorescence analysis on a flow cytometer - immunophenotyping)[13]. Reference values were the following: CD23 (0–8%), CD21 (12.6 3.8%), and HLA-DR (10–32%).

Statistics

The results were statistically analyzed. Tables of frequency, mean values and standard deviations were determined for all parameters studied. The ^{2}-test and Mann-Whitney's test were used to evaluate group differences ($p<0.05$). Statistically significant differences between the two groups according to different parameters are marked with an asterisk (*). Centile distribution of each parameter in patients with »pure« AD and »mixed« AD and HC was also analyzed.

Results

The results obtained showed an almost equal sex distribution of AD patients (16 female and 14 male) (Table 1). Concerning the age at onset, the early infancy was found to prevail; 15 (50%) patients developed the disease under the age of 2, and six patients between 2 and 5, while nine patients had a later onset of the disease. The age at onset was younger in patients with »mixed« AD than in those with »pure« AD. The difference was statistically significant. Twenty (66.6%) AD patients had a history of RA (»mixed« AD), whereas the remaining ten (33.3%) had no history of RA (»pure« AD). Seventeen (56.6%) patients had coexistence of one allergic disease, while three (10%) patients had two coexistent conditions (AR and AB). Family history was positive for atopy in 22 (73.3%) AD patients, in 14 (46.6%) of them in a first-degree relative.

Respiratory allergies were found in 20/30 (66.6%) AD patients allergic rhinitis/conjunctivitis in 12/30 (40%), allergic bronchitis/asthma in 11/30 (36.6%), and a combination of both in 3/30 (10%) (Table

1). However, out of 30 AD patients, 10 (33.3%) had »pure« AD, and 20 (66.6%) suffered from a »mixed« type with concomitant RA (Table 1).

Table 1 shows that most of AD patients – 22/30 (73.3%) had positive family history of allergic diseases and positive first-degree relatives in 14 (46.6%) cases. Patients with »pure« AD had a lower rate (6/10) of respiratory allergic diseases in family history than those with »mixed« AD (16/20) (Table 1).

The severity of diseases is illustrated in Table 2, and parental history in Tables 2 and 3. Patients with »mixed« AD had a higher rate of positive parental history (9/20) than those with »pure« AD (2/10) (Table 2). The results showed that there was no patient whose both parents had RA (Table 3).

According to prick test results, the rate of positive reactions was not greater in patients with »mixed« AD than in those with »pure« AD (Table 4). Patients with AD had positive prick test results in 24 out of 30 cases (80%) (Table 4). Nine (90%) of ten patients with »pure« AD and 15 (75%) out of 20 patients with »mixed« AD had positive prick test (Table 4). The most common positive reactions were to house dust, followed by grass pollen and feather (Table 5). Quite unexpectedly,

TABLE 1
CLINICAL AND HISTORY DATA OF AD PATIENTS AND HEALTHY CONTROLS

	Total AD (N=30)	»Pure« AD (n=10)	»Mixed« AD (n=20)	Healthy controls (N=10)
Male: Female	14:16	6:4	8:12	4:6
Mean age	18:6	18:8	18:5	18:7
*Age at onset (yrs)				
< 2	15	2	13	0
2–5	6	3	3	0
> 5	9	5	4	0
Associated RA	20	0	20	0
One disease	17	0	0	0
Allergic rhinitis/conjunctivitis (AR)	12	0	12	0
Allergic bronchitis/asthma (AB)	11	0	11	0
Other	0	0	0	0
2 diseases	3	0	3	0
None	10	10	0	0
Family history				
Positive	22	6	16	0
1st degree	14	2	12	0
2nd degree	8	4	4	0
Negative	8	4	4	0

*Statistically significant difference

TABLE 2
SEVERITY OF AD ON CLINICAL EXAMINATION AND PARENTAL HISTORY IN 30 AD PATIENTS

AD severity / Parental history	Total (N=30)		»Pure« AD (n=10)		»Mixed« AD (n=20)	
	14 male	16 female	6 male	4 female	8 male	2 female
Mild	3	3	1	2	2	1
Moderate	9	12	4	2	5	10
Severe	2	1	1	0	1	1
Negative	19	8	11			
Positive	11	2	9			
maternal history	9	1	2			
paternal history	2	1	1			

TABLE 3
ATOPIC DISEASES IN PARENTAL HISTORY OF 30 AD PATIENTS

Parental history	Parental history			
+	Negative	Positive	Single	Double
AD	25	5	5	0
AR	24	6	6	0
Asthma	29	1	1	0
Total (N=30)	19	11	11	0

TABLE 4
CUTANEOUS TEST RESULTS IN AD PATIENTS

	Prick test			Scratch test			Patch test		
	Total (N=30)	«Pure« AD (n=10)	«Mixed« AD (n=20)	Total (N=30)	«Pure« AD (n=10)	«Mixed« AD (n=20)	Total (N=30)	«Pure« AD (n=10)	«Mixed« AD (n=20)
Negative	6	1	5	14	6	8	11	5	6
Positive	24	9	15	16	4	12	19	5	14

food allergens were found to predominate over aeroallergens in prick tests as could not be expected (aeroallergens in 6/10 in »pure« AD, and 13/20 in »mixed« AD; food allergens in 8/10 in »pure« AD, and 14/20 in »mixed« AD). Positive reactions to preservatives and additives were observed in 16 patients (4/10 in »pure« AD and 12/20 in »mixed« AD) (Table 4). The highest rate of positive reaction was recorded for acetylsalicylic acid (Table 6). Nineteen out of 30 AD patients showed positive patch test reactions with the standard series of contact allergens. The most common positive reactions were those to nickel (12 patients), bichromate (10) and charcoal tar (9) (Table 7). All healthy controls had negative personal and family history of the disease, and negative skin tests.

The values of IgE were mostly increased (Table 8). Patients with »pure« AD

TABLE 5
MOST COMMON POSITIVE PRICK TEST RESULTS TO ALLERGENS IN AD PATIENTS

Allergen	Total (N=30)	»Pure« AD (n=10)	»Mixed« AD (n=20)
House dust	20	7	13
Grass pollen	14	5	9
Phleum pratense	2	1	1
Dactylis glomerata	1	1	0
Poa pratensis	1	1	0
Feather	10	4	6
Straw	9	4	5
Flour	8	1	7
wheat flour	5	3	2
barley flour	2	1	1
maize flour	1	1	0
Coffee	8	3	5
Mite *(Dermatophagoides pteronyssinus)*	7	3	4
Bean	7	3	5
Pea	7	2	2
Hemp	6	4	2
Cocoa	6	2	4
Animal hair	6	0	6
Tree pollen	5	2	3
Milk	5	1	4
Sea herb	4	0	4
Soya beans	4	1	3
Parsley	3	0	3

showed increased values of IgE in 7/10 (70%) cases, similarly to those with »mixed« AD 14/20 (70%) . The prevalence of IgE increase was not greater in patients with »mixed« AD compared to those with »pure« AD. In both patient groups, serum IgE level mostly exceeded the normal limits, however, the difference between groups did not reach statistical significance. Accordingly, patients with »mixed« AD generally had higher IgE values[6].

Determination of CD23 marker on B-lymphocytes showed normal values in

TABLE 6
NUMBER OF AD PATIENTS WITH POSITIVE SCRATCH TEST RESULTS TO SPECIFIED ALLERGENS

Allergen	Total (N=30)	»Pure« AD (n=10)	»Mixed« AD (n=20)
Acetylsalicylic acid	12	1	11
Potassium metabisulfate	10	3	7
Sodium benzoate	7	2	5
Tartrazine	7	4	3

24, and increased values in six patients (2/10 in »pure« AD, and 4/20 in »mixed« AD). The values of CD21 were decreased in 16 AD patients (6/10 in »pure« AD, and 10/20 in »mixed« AD). Normal values of HLA-DR were recorded in almost all patients (29 patients had normal values and one patient had a decreased value). All healthy controls had normal values of CD23, CD21 and HLA-DR.

The results obtained yielded no statistically significant difference between the two groups according to any of the parameters examined, except for the age at onset of the disease (Tables 1, 8). Centile distribution of skin test results and number of allergens showed similar values in the two groups, with no significant difference between them. The same was observed for CD21 and CD23 markers on B-lymphocytes, and for HLA-DR on T-lymphocytes. So, the values of the majority of parameters differed, however, with no regular changes in their distribution. It is important to note that the sample was small, so the results cannot be considered representative. However, the results showed a statistically significant difference only for the age at onset, while other parameters would obviously require a greater study sample for reveal the possible regularity of changes.

TABLE 7
MOST COMMON ALLERGENS IN POSITIVE EPICUTANEOUS TEST RESULTS IN 30 AD PATIENTS

Allergen	No. of patients with positive reaction	»Pure« AD (n=10)	»Mixed« AD (n=20)
Nickel sulfate	12	3	9
Potassium bichromate	10	3	7
Charcoal tar	9	2	7
Cobalt chloride	8	2	6
Fragrance mix	7	1	6
Balsam of Peru	4	0	4
Carba - compounds	4	2	2
Black rubber mix	2	0	2
Anaesthesyn	2	0	2
»Rubel« detergent	1	0	1
Colophony	1	0	1
»Vim« detergent	1	0	1

TABLE 8
IN VITRO TEST RESULTS IN »PURE« AD AND »MIXED« AD PATIENTS

Parameter	Values	Total (N=30)	»Pure« AD (n=10)	»Mixed« AD (n=20)
IgE	Normal (–150)	9	3	6
	151–300	4	2	2
	> 300	17	5	12
CD21	Decreased	16	6	10
	Normal (–150)	13	4	9
	Increased	1	0	1
CD23	Normal	24	8	16
	Increased	6	2	4
HLA-DR	Decreased	1	0	1
	Normal	29	10	19

Although the assessment of most parameters (skin tests, IgE, and CD21, CD23 and HLA-DR markers) yielded no statistically significant difference between the two groups, some conclusions could be drawn. Thus, the minimal IgE values were considerably lower in patients with »pure« AD than in those with »mixed« AD. Furthermore, the majority of centile values of other parameters were higher in patients with »pure« AD than in those with »mixed« AD. The values of HLA-DR were higher in »pure« AD patients than in »mixed« AD patients and healthy controls. The values in centile distribution showed an upward shift in patients with »pure« AD compared with patients with »mixed« AD. No statistically significant difference was observed in the analysis of CD21, CD23 and HLA-DR values, although in some centile distribution patterns they were higher in

»mixed« AD patients than in »pure« AD patients.

However, there was no statistically significant difference ($p<0.05$) between the »pure« AD and »mixed« AD patient groups, except for the age at onset, which was younger in the group of patients with concomitant RA.

Discussion

According to the literature, nearly a half of AD patients show clinical signs of concomitant respiratory allergies (»mixed« AD)[1–3]. Thus, Hanifin and Rajka found manifestations of RA in roughly 50% of AD patients[3]. Similarly, Diepgen and Fartasch found »mixed« AD in 46% of patients with AD[12]. Wüthrich found that about 60% of patients with AD had associated RA[7]. We found respiratory allergies in 20/30 (66.6%) AD patients and »pure« AD in 10/30 (33.3%) of the patients, which is consistent with literature data. Sampson reported on concomitant atopic diseases in 80% of AD patients: allergic rhinitis in 25%, asthma in 10%, both asthma and allergic rhinitis in 45%, and neither of the two in 20%[14].

Of course, the figures vary with the age of the population: e.g., many infants with AD may not develop respiratory symptoms until much later[3]. One fourth to one third of AD children will have respiratory symptoms as well as skin manifestations of AD[15]. It is the patient with both respiratory and skin symptoms who tends to have more severe diseases, both respiratory and cutaneous, and a poorer prognosis for both[15]. Our study showed a statistically significant difference in the age at onset between the »pure« AD and »mixed« AD group, with an earlier onset in the »mixed« AD group. Patients with concomitant RA had a younger age at onset than those with »pure« AD. It may indicate that an early onset of AD often brings concomitant RA, and that infants with very early signs of AD are candidates for the manifestation of RA[16,17]. So, when working with small children with AD, physicians should borne in mind that there is a high probability that they would develop RA later in life. Hochreutener showed clinically relevant respiratory allergy in 15% of AD children (rhinoconjunctivitis in 10%, inspiratory stridor in 2.5% and bronchial asthma in 15% of AD children)[18]. Larsen et al. often found asthma in personal history of boys (6.1%), and in family history of girls (11.7%)[19]. Hanifin and Rajka found one or more manifestations of atopy in family history in approximately 70% of AD patients[3].

In allergic asthma and allergic rhinitis, the causative allergens can often be found, but allergens causing or worsening skin conditions can seldom be detected in AD[7]. There are different attempts to determine allergic reactions of type I: by means of skin tests (early hypersensitivity tests), specific IgE determination by RAST or ELISA, specific provocation tests, etc.[20] The results vary and the percentage of positive skin test reactions ranges from 50% to over 90%[1–7]. Some authors report that AD patients with AB or AR (»mixed« AD) show significantly more frequent positive test reactions to inhalant allergens, particularly house dust, house dust mites, pollen, and animal allergens (animal hairs and scales) than other subjects[1]. Even if no concrete concepts exist about the causal significance of inhalant allergens in the precipitation or exacerbation of AD, it is possible that seasonal phases of AR can be related to a deterioration of the skin disesase, and *vice versa*. The pathogenic role of other environmental inhalant allergens is rather difficult to demonstrate, because of the widespread and perennial occurrence of house dust mites and moulds, and frequent polyvalent IgE sensitization. In our study, skin tests to the

standard series of inhalant allergens identified aeroallergens as the most common allergens causing skin allergy. It is interesting that some AD patients exhibited no evidence of positive allergic reactions to some allergens, although they had AD. We also observed some patients with »mixed« AD who showed no evidence of positive prick test to at least one allergen, although they clinically had AD with concomitant RA, characteristic of a strong atopic status.

Atopic dermatitis, asthma and AR are commonly classified as atopic diseases, because the increased levels of IgE in the serum have been proposed as a common etiologic factor[20,21]. The IgE response is so far a facultative attribute of AD and according to Hanifin and Rajka only a minor diagnostic criterion. Patients with »pure« AD in 20%–40% do not have increased total IgE and specific IgE[7]. However, one should borne in mind that in 20%–40% of »pure« AD cases neither elevated IgE levels nor specific IgE sensitization can be found[7]. Serum IgE level is raised in a majority of patients with severe AD[1]. Some authors found the IgE levels to be more often increased in AD patients with concurrent respiratory tract manifestations (allergic asthma, allergic rhinitis)[7]. Van Voorst Vader et al. found elevated median serum IgE in patients with »mixed« AD compared with the median serum IgE in »pure« AD[22]. We found increased levels of IgE in seven out of 10 (70%) patients with »pure« AD, and in 14 out of 20 (70%) patients with »mixed« AD, and no difference between the two groups indicating no changes of the allergologic status in »mixed« AD. However, as the serum IgE level may be within the normal limits even in some paients with extensive skin lesions, the determination of IgE level is of no pathognomonic significance. In some AD patients, exacerbation of asthma may cause that the skin lesions seem to disappear, and *vice versa*[2]. In Ring's investigation, only 10% of patients with AD exhibited an alternating pattern of the diseases[2]. Some patients, however, clearly showed a coincidental exacerbation of both skin lesions and respiratory symptoms during allergen exposure[2]. However, the association of AD and RA may be evident[23–26].

Delayed hypersensitivity type IV (cell-mediated immunity) is considered to be involved in the pathogenesis of AD[27–33]. Therefore, determination of the cells and their markers (e.g., CD23) could be of importance for the disease. In some recent studies it has been indicated that a low-affinity IgE receptor, FcRII (CD23), has an important role in the pathogenesis of AD. The expression of CD23 receptors on the peripheral blood mononuclear cells (PBMC) was analyzed in AD patients[34–36]. Some authors showed an increased CD23 positive lymphocyte count in allergic patients as compared with controls[13]. Takigawa et al. examined the effect of personal RA on the frequency of expression of CD23 receptor, and concluded that the presence of personal respiratory allergy *per se* did not influence the frequency of CD23+ PBMC8. Allergic patients were found to have elevated CD23 as well as CD21 when compared with controls[13,35]. There also was a positive correlation between CD23 and total serum IgE levels in allergic children[13,35]. These results stress the role of the CD21-CD23 ligand-pair interaction in IgE-mediated diseases[13,35,36]. Determination of HLA-DR markers on peripheral blood T-lymphocytes, performed in our study, showed normal values in almost all AD patients, although activated (HLA- DR+) T-lymphocytes predominated in the dermal infiltrate.

It is commonly considered that RA is often the reason for inducing skin lesions in AD, but our study showed no difference in the allergologic parameters and status between AD patients with and without concomitant RA. Future studies may ho-

pefully provide more data on the pathogenesis of this fascinating disease, and entail some important implications for the treatment of the different manifestations of the atopy syndrome.

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JESU LI RESPIRACIJSKE ALERGIJSKE BOLESTI POVEZANE S ATOPIJSKIM DERMATITISOM?

S A Ž E T A K

Razlika u rezultatima testova između bolesnika s »čistim« atopijskim dermatitisom (AD) i »miješanim« AD-om (s pratećom respiracijskom alergijom, RA) istraživala se u 30 bolesnika s AD-om. Rezultati su pokazali da se bolest većinom javlja u ranoj dječjoj dobi u 15 (50%) bolesnika do 2. godine - 2/10 u »čistom« AD-u, a 13/20 u »miješanom« AD-u . Dvadeset (66,6%) bolesnika je imalo RA u anamnezi (»miješani« AD), dok je ostalih 10 (33,3%) imalo »čisti« AD. Sedamnaestero (56,6%) bolesnika s AD-om imalo je još jednu alergijsku bolest, dok je troje (10%) imalo po dvije alergijske bolesti (AR i AB). Atopija u obiteljskoj anamnezi je zamijećena u 22 (73,3%) bolesnika s AD-om 14 (46,6%) bolesnika u bližem srodstvu . Dvadesetčetvoro (80%) bolesnika je imalo pozitivan ubodni test 9/10 (90%) u »čistom« AD-u, a 15/20 (75%) u »miješanom« AD-u , najčešće na kućnu prašinu (20). Pozitivan skarifikacijski test je zabilježen u 16 (53,3%) bolesnika 4/10 u »čistom« AD-u, a 12/20 u »miješanom« AD-u . Devetnaestoro (63,3%) bolesnika s AD-om je imalo pozitivan *patch* test 5/10 u »čistom« AD-u, a 14/20 u »miješanom« AD-u . Bolesnici s AD-om su imali više vrijednosti serumskog IgE-a (21/30) od neatopičara, ali slične u »čistom« i »miješanom« AD-u 7/10 (70%) u »čistom« AD-u, a 14/20 (70%) u »miješanom« AD-u . Određivanja biljega CD23 na B-limfocitima su pokazala normalne vrijednosti u 24, a povišene u šestoro bolesnika (2/10 u »čistom« AD-u, a 4/20 u »miješanom« AD-u). Vrijednosti CD21 većinom su bile snižene - u 16 bolesnika s AD-om (6/10 u »čistom« AD-u, a 10/20 u »miješanom« AD-u). Ekspresija HLA-DR je bila u granicama normale u gotovo svih bolesnika. Nije uočena statistički značajna razlika ($p<0,05$) između skupina bolesnika s »čistim« AD-om i »miješanim« AD-om, osim u dobi početka bolesti koja je bila niža u bolesnika s pratećom respiracijskom alergijom. Dakle, postoji povezanost između AD-a i RA.