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Allergic diseases, drug adverse reactions and total immunoglobulin E levels in lupus erythematosus patients

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***Background*: The association of allergic diseases, drug adverse reactions and elevated total immunoglobulin E (IgE) concentration in systemic lupus erythematosus patients remains controversial. The aim of the study was to investigate the prevalence of those features in active and inactive systemic lupus erythematosus patients, and in the control group as well.**

***Methods*: Total IgE concentration was evaluated by enzyme-linked immunosorbent assay**

***Results and conclusions*: The results of our study revealed that concomitant allergic diseases were not more frequent in systemic lupus erythematosus patients than in the general population. Total IgE concentration was significantly higher during the active stage of the disease. Drug reactions were very frequent but not connected with IgE elevation. Our results indicate that IgE may play a role in lupus pathogenesis, especially in the active phase of the disease.**

Key words: Systemic lupus erythematosus, Allergy, Immunoglobulin E

Introduction

Systemic lupus erythematosus (SLE) remains elusive in the description of its underlying etiologic causes and pathogenic mechanisms. Although genetic predisposition appears to contribute to the disease based on twin and genetic studies, additional factors like viral and bacterial infections, ultraviolet exposure, diet, toxins (environmental), and hormonal abnormalities must play a role.[1]

Allergy and SLE share some pathophysiological mechanisms. In both disorders, dysregulation of the immune system, especially B-cell hyperactivity, leading to production of various types of immunoglobulins, plays an important role.[2]

The literature data concerning the relationship between diseases with allergic background and SLE, as well as the contribution of immunoglobulin E (IgE) to lupus pathogenesis, remain controversial. Therefore the aim of the study was to investigate the prevalence of asthma, allergic rhinitis, atopic dermatitis, urticaria and drug reactions as well as total IgE serum level in various subgroups of SLE patients.

Materials and methods

The study involved patients with SLE who attended, out-patient and in-patient, Department of Dermatology, Medical University of Lodz between 1998 and 2002. The diagnosis of SLE was based on the revised criteria of the American Rheumatism Association (now known as the American College of Rheumatology).[3]

At the time of the study, each patient underwent a thorough physical examination. The following laboratory parameters were analysed: complete blood cell count, erythrocyte sedimentation rate, urinalysis, blood urea, creatinine and fibrinogen levels, C reactive protein, liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin), antinuclear antibodies and lupus band test.

Disease activity was scored according to the method described by Liang *et al*.[4] The scale of Systemic Lupus Activity Measure (SLAM) includes 24 clinical symptoms and eight laboratory parameters. The maximum score in this system is 84 points. In the present study, a score between 0 and 15 points was considered as an inactive disease and above 15 points as an active disease.

Only patients who were not treated with immunosuppressive agents, high doses of steroids or antihistamines drugs were included in the study. None of the subjects had symptoms of viral or parasitic infection during the study based on clinical examination and the results of laboratory tests already mentioned.

The patients and controls were interviewed to determine the presence of atopic dermatitis, allergic rhinitis, asthma, family history of atopy, urticaria,

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drug reactions, and contact dermatitis according to Goldman *et al*.[5] Moreover, the diagnosis of asthma, allergic rhinitis and atopic dermatitis was previously established by a general practitioner or a specialist in allergy based on appropriate criteria and diagnostic tests.

Total IgE concentration was evaluated in patient sera as well as in age-matched and sex-matched healthy persons by enzyme-linked immunosorbent assay using the commercially available UniCAP Total IgE kit (Pharmacia α Upjohn Diagnostic AB, Uppsala, Sweden) according to the manufacturer's instruction. In five patients, the IgE level was controlled twice during remission and flare of the disease.

In patients with inactive disease and history of skin rash, which may have suggested allergic contact dermatitis, patch tests were also performed with the European Standard (S-100; Chemotechnique Diagnostics, Malmo, Sweden) with a 48-h application time and readings at 48, 72 and 96 h. The patients were not treated with corticosteroids or immunosuppressive agents either systemically or topically at least 6 weeks before testing.

The study was performed in accordance with the Helsinki Declaration and approval of the local Ethics Committee. Informed consent was obtained from all patients participating in the study.

Statistical analysis

For the statistical analysis of the data, the range of measured variables is given (minimum–maximum). The arithmetic mean values (x), median (Me) and standard deviation (SD) have also been calculated. The Shapiro–Wilk's test was used to evaluate the distribution. The comparison of variable values in groups was performed depending on the distribution of features of the Mann–Whitney test, or the test for two means for independent samples or the Cochran–Cox test.

Results

The study involved 72 Caucasian patients (67 females and five males), aged 20–76 years (mean, 37 years). The mean duration of the disease was 5 years (range, 1 month–20 years). The patients' characteristics are presented in Table 1.

Active disease was found in 24 patients, while 48 patients were in an inactive stage of SLE. During the time of the study six patients were used anti-malarial drugs and seven non-steroid anti-inflammatory agents. Patients who were in the active stage of the disease donated blood before their treatment was changed to a more aggressive one. Allergic diseases were present in 14 out of 72 patients. The most frequent diagnosis was allergic rhinitis (10/72); less frequent was atopic dermatitis (2/72) and acute urticaria (2/72). More than one atopic disease was diagnosed in two patients. Asthma was diagnosed in none of the patients.

Table 1. The SLE patients' characteristics

Parameter	Study group ($n = 72$)	Percentage (%)
Women	67	93
Men	5	7
Age (years)	20–76 (mean, 37)	–
Duration of SLE (years)	0.1–20 (mean, 5)	–
Active SLE	24	33.3
Inactive SLE	48	66.7
Allergic diseases (all)	14	19.4
Atopic dermatitis	2	2.8
Alergic rhinitis	10	13.8
Urticaria	2	2.8
Asthma	0	0
Family history of allergy	20	27.8
Drug reactions	26	36.1
Patch tests performed	27	38.8
Patch tests positive	7	9.7

The total IgE concentration in the SLE group ranged from 2 to 4015 IU/ml (Me = 45.5 IU/ml) and was significantly higher ($p = 0.028$) than in the comparable 31 healthy controls, in whom those values ranged from 3 to 151 IU/ml (Me = 24 IU/ml) (Table 2). The total IgE concentration in 14 SLE patients with coexistent allergic diseases ranged from 80 to 4015 IU/ml (Me = 172 IU/ml) and was statistically higher than those values in 58 patients without concomitant allergic diseases, which ranged from 2 to 502 IU/ml (Me = 35 IU/ml; $p = 0.009$) and the control group (range, 3–151 IU/ml; Me = 24 IU/ml; $p = 0.001$). In contrast, the values of total IgE in patients without allergic diseases and controls did not differ statistically. The highest total IgE concentration (mean = 2111 IU/ml) was noted in group of patients with SLE and concomitant atopic dermatitis.

A family history of atopy was reported in 20 out of 72 SLE patients (28%). In those subjects, allergic rhinitis and asthma were particularly frequent. The total IgE level in patients with atopic diseases in their families ranged from 3 to 4015 IU/ml (Me = 65.5 IU/ml) and, although it was higher than in patients without this disorder (2–502 IU/ml, Me = 37 IU/ml), the difference was not statistically significant ($p > 0.05$).

The total IgE concentrations were compared in different stages of the disease activity (Table 3). The IgE serum level in 24 patients in the active phase of the disease ranged from 5 to 1166 IU/ml (Me = 152.5 IU/ml) and was significantly higher than in 48 patients during remissions, in which the respective values ranged from 2 to 4015 IU/ml (Me = 31.5 IU/ml; $p = 0.003$), and in controls (range, 3–151 IU/ml;

Table 2. Total IgE concentration in SLE patients with and without allergy and in control group

	Total IgE concentration (IU/ml)				Statistical significance
	All SLE patients ($n = 72$) (a)	SLE patients with allergic diseases ($n = 14$) (b)	SLE patients without allergic diseases ($n = 58$) (c)	Control group ($n = 31$) (d)	
Median	45.5	172.0	35.0	24.0	(a)–(d), $p = 0.028$
Range	2.0–4015.0	80.0–4015.0	2.0–502.0	3.0–151.0	(b)–(c), $p = 0.009$
Mean ± SD	172.3 ± 494.1	509.0 ± 1053.4	91.0 ± 128.0	36.9 ± 38.9	(b)–(d), $p = 0.001$
					(c)–(d), $p > 0.05$

Me = 24 IU/ml; $p = 0.0002$). There were no statistically significant differences in IgE concentration between inactive SLE patients and the control group.

In five patients aged 20–50 years, the total IgE levels were evaluated in the inactive phase and during lupus flares. The IgE concentration during remissions ranged between 34 and 150 IU/ml (mean = 98.6 ± 41.6 IU/ml, Me = 100 IU/ml) and was statistically significantly lower ($p < 0.005$) than during active phase of the disease, where the respective values ranged between 172 and 306 IU/ml (mean = 240.4 ± 64.3 IU/ml, Me = 250 IU/ml).

Drug reactions were noted in 26 out of 72 analysed SLE patients. Urticaria, oedema, rashes and anaphylactic reactions were most often caused by antibiotics. These types of reactions were noticed in 15 patients. Penicillin/cephalosporin (10 cases), gentamycin (two cases), and tetracyclin (three cases) were the main cause of drug reactions. Less frequently, non-steroid anti-inflammatory drugs (four cases), sulphonamides (three cases) and sulphones (two cases), codeine (one case) and pentoxifylline (one case) were noted. Four patients reported that these symptoms were caused by more than one drug. At the time of the study, it was not possible to establish the exact mechanism of each drug adverse reaction.

Exacerbations of the disease (lupus flares) were confirmed by physicians as related to the drug only in four of 72 patients. Total IgE concentrations in SLE patients with drug reactions ranged from 2 to 518 IU/ml (Me = 40.5 IU/ml) and were not statistically different compared with the respective values in SLE patients without drug reactions (range, 2–4015 IU/ml; Me = 49.1 IU/ml; $p > 0.05$).

Patch tests that were performed in 27/72 (37.5%) patients aged 21–57 years (mean = 38 years) with history, which may have suggested contact dermatitis, revealed allergic reactions to at least one allergen in seven. There were four reactions to nickel (14.8%), two reactions to chromate (7.4%), two to fragrance mix (7.4%), two to wool alcohols (7.4%), two to mercaptobenzothiazole (7.4%), and a single reaction to benzocaine, cobalt, phenylenediamine and neomycin. Reactions to six allergens were observed in a patient with antiphospholipid syndrome and a long history of leg ulcer.

Discussion

The frequency of allergic diseases and total IgE concentration in SLE patients were analysed by several authors but until now some controversies have remained. Goldman *et al*.[5] were the first who documented that in the SLE group allergic rhinitis and drug allergy had higher incidence, although IgE levels were not different from those in healthy population. Sequeira *et al*.[6] found that 132 patients with SLE had significantly higher numbers of drug, skin and insect allergies than 66 individuals with non-SLE disorders.

There were also some attempts to explain why patients with lupus have more allergies. Diumenjo *et al*.[7] postulated a higher level of hypersensitivity to exogenous antigens through anaphylactoid products of complement activation. Gruber *et al*.[8] found IgM–anti-IgE (in 27%) and IgG–anti-IgE (in 34%) antibodies in 67 patients with SLE.

The results of our study revealed concomitant allergic diseases in 19% of patients, which is not higher than in general population of inhabitants in our region (22.2%).[9] Our observations are in line with those obtained by Morton *et al*.,[10] who revealed no significant differences in frequency of allergic disorders in 49 SLE cases and 98 controls. Results presented by Shahar and Lorber[11] exposed signifi-

Table 3. Total IgE concentration in active and inactive SLE patients

	IgE concentration (IU/ml)			Statistical significance
	Active SLE patients ($n = 24$) (a)	Inactive SLE patients ($n = 48$) (b)	Control group ($n = 31$) (c)	
Median	152.5	31.5	24.0	(a)–(b), $p = 0.003$
Range	5.0–1166.0	2.0–4015.0	3.0–151.0	(a)–(c), $p = 0.0002$
Mean ± SD	209.6 ± 253.0	153.6 ± 579.9	36.9 ± 38.9	(b)–(c), $p > 0.05$

cantly higher incidence of allergic diseases in SLE patients; especially, rhinitis (34%) and asthma (47%) were present more often than in our examined group.

The discrepancy of the obtained data may be connected not only with immunological abnormalities in lupus patients, but also with the geographical differences. The outcomes of the European Community Respiratory Health Survey indicate dissimilarities in the frequency of allergic diseases in various regions in the world, and pointed at the higher incidence of allergic disorders in industrial countries.[12]

The role of E immunoglobulins in immune complex diseases has not been fully investigated. Some authors claim that IgE, through the release of vasoactive mediators from basophils and mast cells, can cause increased vasopermeability, which may be important in creating deposits of circulating complexes in glomerulonephritis.[13] Others, however, state that patients with SLE are not at increased risk of IgE-mediated allergic disorders.[10]

Although in our group of 72 patients the total IgE concentration was significantly higher than in controls, it seems that it was rather connected with concomitant allergic diseases than with SLE by itself. The lack of statistically significant differences between the IgE level in SLE patients without allergy and the control group supports this statement.

Our previous investigations, performed only in SLE patients during remission, revealed that the higher IgE levels were connected with concomitant atopic diseases and they were not related to SLE. In inactive patients, without simultaneous atopic diseases, the IgE level was not different from that in the general population.[14]

The aetiology of SLE is complex, and hereditary factors play also an important role in the disease pathogenesis. Sasai *et al*.[15] found the higher prevalence of allergic diseases in children of mothers with SLE. In our group, the frequency of atopic diseases (28%) in blood relatives of the patients was higher than the frequency of these diseases in the general population.[9]

There are literature controversies concerning the involvement of the reagin-type antibodies in autoimmune diseases. Some authors postulate that IgE is not related to the connective tissue diseases,[16] but others suggest that they might play an essential role.[17] Rebhun *et al*.[18] suggest that IgE antibodies may mediate the release of chemical mediators and facilitate local deposition of immune complexes, and even though the IgE levels were between the normal range the evidence is highly suggestive that the increase of serum IgE accompanies disease activity in most patients. The mean value of the IgE concentration in SLE active patients was more than three times higher than in inactive patients. The authors investigated also a group of five patients both in flares and in remission, and noticed the elevation of the IgE level during exacerbation of the disease. IgE antibody might be responsible for the activation of mast cells in SLE patients for the release of chemical mediators, especially histamine. The knowledge of these associations is important from the therapeutic point of view, as the antihistaminic drugs may be helpful in the treatment of the disease flares.[18]

The relationship between serum IgE concentrations and SLE activity has also been investigated. In our group the highest total IgE levels were noted in active SLE patients in whom those values were significantly higher in comparison with inactive patients as well as with the control group ($p = 0.003$ and $p = 0.0002$, respectively). There were no statistical differences between the inactive group and controls, which additionally supports the argument that IgE plays a role in active stages of the disease. Our results are in agreement with Elkayam *et al*.,[19] who found a statistically significant higher level of this immunoglobulin in SLE patients during lupus flares. Those authors stressed that the highest IgE levels were detected in patients with lupus nephritis. Only five patients in our group were observed during flares (> 15 according to SLAM score) and remissions (< 15 points). In all of them, significantly higher IgE concentrations were noted during exacerbations of the disease.

Some authors claim that in SLE patients the IgE level cannot be regarded as a reliable feature of SLE activation because multiple factors influence IgE production.[20] In our opinion, this feature could serve as a prognostic factor because in the whole SLE active group the IgE concentration was significantly higher than in inactive patients, and also in all five monitoring patients during flares of the disease the IgE concentration was significantly higher than in remission.

Environmental agents including drugs are known as provoking and exacerbating factors in SLE patients.[21] The literature data concerning drug reactions in lupus patient also give controversial results. Some authors claim that drug reactions have a similar frequency in SLE patients and healthy volunteers group.[22] Others, however, postulate the increased ratio in the SLE group.[5,23]

In our study, drug reactions were very frequent in SLE patients (36%). A population study performed 2 years ago on the group of 1900 inhabitants of our region revealed drug reactions in 11.4%. This feature was more common in women (14.7%) than in men (8.8%).[24] Our observations are in line with Petri and Allbritton.[23] Similarly to their report, penicillin/cephalosporin were regarded as a main cause of drug reactions in lupus patients. Contrary to their observations, in our patients flares of disease were rarely

connected with drugs. However, it is difficult to diagnose whether the lupus flare is connected with infection or with drug, or is just spontaneous, without any known reason.

The exact mechanism of increased prevalence of drug reactions, especially antibiotic allergy, in lupus patients is not completely understood. One possible explanation of this fact is that SLE patients are more exposed to antibiotics than the general population, which may increase the chance of developing allergy reactions.

There are not many reports regarding the prevalence of allergic contact dermatitis in SLE patients. Goldman *et al*.[5] interviewed 24 patients for a history of contact dermatitis defined as 'erythema and/or vesicles on exposure to simple chemicals'. No differences between the SLE group (9/24, 37.5%) and controls (12/27, 44.4%) were observed. They concluded that the prevalence of contact dermatitis, a cutaneous manifestation of cell-mediated immunity, was similar in both groups. On the contrary, Sequeira *et al*.[6] found that skin allergy was statistically significant more frequent in SLE patients than in controls (36% versus 17%; $p < 0.01$). However, in their study, skin allergy was defined as 'any urticarial or erythematovesicular skin reactions directly related to skin contact with allergens', so contact urticaria as well as irritant contact dermatitis were included in their group. Morton *et al*.[10] interviewed 49 patients with SLE, asking a question about skin reaction to nickel or make-up resulting in redness and/or small blisters, and found positive answers in 28.6% and 8.2% patients, respectively, compared with 41.8% and 10.2% controls. In our study, patch tests were performed to prove allergy contact dermatitis. The results are comparable with the expected frequency of reactions to patch tests in different populations. In the UK, Germany, the USA and Singapore, allergy to nickel was found in 6.7–17.7% cases, to cobalt in 2.0–4.7% and to chromate in 0.9–6.8%.[25] So it seems that the prevalence of allergic contact dermatitis in SLE patients is not higher than in the general population.

Despite many literature controversies and multiple factors influencing IgE production, the obtained results indicate that IgE may play a role in lupus pathogenesis, especially in the active phase of the disease, but further studies are still needed.

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