IgE and non-IgE mediated allergic disorders in systemic lupus erythematosus

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Abstract

***Objective*—To ascertain the prevalence of IgE and non-IgE mediated allergic disorders in patients with systemic lupus erythematosus (SLE).**

***Methods*—49 SLE cases (all satisfying at least four "Revised ARA Criteria") and 98 healthy, age, and sex matched controls (randomly selected through two urban general practices and one rural general practice) were interviewed by telephone to screen for a history of allergy. Subjects with a history of allergic rhinitis, asthma or atopic eczema then underwent skin prick testing to confirm underlying IgE mediated disease.**

***Results*—Analysis of the data by conditional logistic regression revealed no significant difference in frequency of allergic disorders in SLE cases and controls (odds ratio (OR) 0.92, 95% confidence intervals (CI) 0.45, 1.86). In addition a subgroup analysis of subjects with IgE mediated/associated atopic disorders, showed that cases and controls were at a similar risk of having these conditions (OR 0.90, 95% CI 0.41, 1.96).**

***Conclusions*—This study suggests that people with SLE are not at an increased risk of IgE mediated/associated allergic disorders, in contrast with previous reports.**

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After reports of higher rates of allergy in systemic lupus erythematosus (SLE), there has been much interest in the relation between IgE mediated allergy and the pathogenetic mechanisms involved in SLE.[1–4] However, the figures quoted for prevalence of allergy in lupus patients vary considerably between reports,[3 5–11] possibly through the use of differing definitions of allergy, some of which encompass both IgE mediated phenomena as well as allergies that are unrelated to IgE triggering of mast cells (non-IgE mediated). In 1976 Goldman *et al* studied 27 SLE patients and concluded that they were at greater risk of drug induced urticaria, angio-oedema, and anaphylaxis, as well as allergic rhinitis, compared with age and sex matched healthy controls.[5] Shahar *et al*[6] obtained similar results, observing that SLE patients were more likely than controls to report conjunctivitis, rhinitis, asthma, and skin eruptions related to food and drugs. Elkayam, on the other hand, described rates of atopy in SLE patients that were comparable to the general population.[1] Several other authors have since published data on allergy related to drugs; Petri and Allbritton[7] concluding that drug allergy (rashes, hives, angio-oedema, fever, and wheezing) was more common in SLE patients and Sequeira[8] describing increased rates of urticaria, angio-oedema, and anaphylaxis after drug ingestion.

Increased concentrations of IgE have been reported in active lupus, especially lupus nephritis, suggesting a possible role for IgE in the pathogenesis of SLE.[1] Furthermore Gruber *et al* found anti-IgE antibodies in a significant number of patients with SLE[2] and in studies of cytokine profiles[3 4] a plausible link between SLE and allergy has been identified as concentrations of interleukin 4 (IL4), IL5, IL6, and IL10, the so called "TH2" class of cytokines, are increased in both.

In this study we set out to establish for the first time the prevalence of proven IgE mediated/associated disorders such as atopic rhinitis, asthma, and eczema by skin prick testing. We also ascertained the prevalence of urticaria and angio-oedema, two conditions that are not necessarily IgE mediated, so that our results could be compared with published data.

Methods

PATIENTS AND CONTROLS

With local ethics committee approval, 50 patients with SLE, all satisfying at least four revised ARA criteria,[12] were randomly selected from the cohort of 180 patients with SLE attending clinical immunology clinics at the Queens Medical Centre, Nottingham. For every case recruited, two age (year of birth) and sex matched controls were selected through three Nottingham general practices, one rural and two urban. Of the 50 SLE patients, one declined to take part and two could not be contacted so a second randomisation of three subjects was carried out. A total of 181 healthy—non-lupus—people were invited to take part to obtain the requisite number of 100 controls. In most cases the reason for our inability to establish contact with controls, was the provision of incomplete details and outdated telephone numbers from the GP records and only one control subject refused to take part once contacted. Unfortunately because of inadvertent mismatching of one case the final number of patients included in our analysis was 49, with 98 matched controls.

Our study was designed to detect odds ratios of 3–4 for exposure levels of 10–15% using a p value of 0.05 (based on levels of risk reported by Sequiera *et al*[8]).

ALLERGY QUESTIONNAIRE

With verbal consent, a telephone questionnaire was administered by one of us (SM) and

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Table 1 Demographic features and percentage of SLE patients and healthy controls with allergic disorders

Group status	Group size	Sex ratio Female %	Mean age (range)	Allergy positivity(%)*	Allergies/person	Atopy positivity(%)†
SLE case	49	98	45.6 (19.7–75.2)	49	0.63	24.5
Healthy control	98	98	45.4 (19.7–75.2)	51	0.63	26.5

* Allergy positivity: percentage of people with one or more types of allergic disorder (IgE mediated/associated). † Atopy positivity: percentage of people with one or more types of atopic disorder.

although the interviewer was not blinded to the case/control status of the subjects they were all questioned in a standard format. They were asked to respond either "Yes" or "No" to the following questions: (1) Do you suffer from hayfever? (2a) Do you suffer from frequent sneezing attacks, a persistently blocked or running nose and if so (b) is there any pattern to the occurrence of your symptoms, for example, only on contact with dogs? (3a) Do you have asthma or (b) Do you have attacks of wheeze or breathlessness? (4) Do you have, or have you ever had eczema and if so was it of the infantile, flexural sort? (5) Have you ever had a "nettle rash" —that is, itchy raised red rash? (6) Have you ever had an attack of facial/genital/tongue swelling referred to as angio-oedema? (7) Have you ever had an attack of anaphylaxis, resulting in severe breathing difficulties and/or collapse with loss of consciousness (8) Does your skin react to nickel or to makeup, resulting in redness and/or small blisters? (9a) Have you ever been stung by a wasp and if so (b) Did you react badly to it, for example, severe local swelling? (10) Are you allergic to any foods? (11) Are you allergic to any medications? (12) Are you photosensitive/allergic to the sun—that is, do you develop rashes in the sun?

In cases where there was doubt about the existence and/or nature of an "allergy" the subject was asked to describe the type of reaction in some detail and if appropriate, invited to have skin prick tests carried out.

SKIN PRICK TESTING (SPT)

Any person with a history suggestive of asthma, atopic eczema, hayfever/allergic rhinitis underwent SPT with the following aeroallergens: house dust, house dust mite, grass pollen, tree pollen, weed and shrub pollen, and cat or dog dander (all reagents were of a standardised concentration and manufactured by Bencard, Welwyn Garden City, Hertfordshire). Skin prick tests were carried out only after antihistamines had been withdrawn for at least 48 hours and all tests were performed by the same investigator according to a standardised procedure, the "modified skin prick test" technique.[13]

Subjects were categorised as having allergy of different types according to the definitions shown below:

IgE mediated atopy

1 Allergic asthma; asthma or wheeze triggered by a specific agent, associated with positive SPTs.

2a Hayfever; suggestive history supported by positive SPTs to pollens.

2b Allergic rhinitis; history (blocked nose, running nose, frequent sneezing attacks) associated with positive SPTs to aeroallergens other than pollens.

IgE associated atopy

3 Atopic eczema; eczema affecting flexural kin, starting in infancy and lasting for several years +\− positive SPTs.

Probable IgE mediated allergy

4 Insect allergy; severe localised reaction (swelling +/− erythema), urticaria, angio-oedema or anaphylaxis after a bee or wasp sting.

Possible IgE mediated allergy

5 Skin allergy; non-physical urticaria.

6 Food allergy; urticaria, angio-oedema or anaphylaxis. (Food intolerance is a separate entity and was defined as any adverse reaction to food that could be explained in terms of an abnormal sensitivity to normal components, for example, histamine in strawberries).

7 Drug allergy; urticaria, angio-oedema or anaphylaxis related to a specific drug. All other self reported, possible, drug related adverse effects were categorised as "drug reactions", for example, vomiting, headache, non-urticarial rashes.

The prefixes "probable" and "possible" have been used with reference to insect, skin, food and drug allergy for reasons described in the Discussion. People with contact dermatitis and photosensitivity were not included in our definition of allergy because they are classically not a consequence of IgE mediated mast cell degranulation.

DATA ANALYSIS

Matched case-control odds ratios (OR) and their 95% confidence intervals (CI) were calculated by conditional logistic regression using EGRET (Version 1.2.9, SERC and CYTEL).

Results

Twenty four of 49 SLE patients (49%) and 50 of 98 (51%) healthy controls had at least one type of allergic disorder and there was no statistical difference between them (OR=0.92, 95% CI=0.45, 1.8, p=0.81). There was also no difference in the average number of allergies reported by individual cases and controls (table 1).

Table 2 illustrates the prevalence rates of different allergy types in SLE cases and controls. For the purpose of comparison with previous studies data on contact dermatitis were included.

Patients with SLE were 4.27 times more likely to describe one or more adverse drug reactions (95% CI 1.78, 10.23, p < 0.001) but

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Table 2 Frequency of different allergy types in SLE cases and controls

Allergy	*Type*	*SLE n (%)*	*Controls n (%)*	*Odds ratio*	*95% CI*	*p Value*
IgE mediated/associated	Allergic asthma	4 (8.2)	8 (8.2)	1.00	0.30, 3.32	NS
	Hayfever	6 (12.2)	13 (13.3)	0.90	0.30, 2.67	NS
	Allergic rhinitis (not due to pollen)	8 (16.3)	14 (14.3)	1.38	0.53, 3.57	NS
	Hayfever and allergic rhinitis	11(22.4)	22 (22.4)	1.00	0.45, 2.23	NS
	Atopic eczema	4 (8.2)	8 (8.2)	1.00	0.29, 3.50	NS
Probable IgE mediated	Insect allergy	3 (6.1)	11 (11.2)	0.50	0.06, 4.47	NS
Possible IgE mediated	Skin allergy*	8 (16.3)	15 (15.3)	1.16	0.32, 4.22	NS
	Food allergy †	2 (4.1)	2 (2.0)	2.00	0.28, 14.2	NS
	Food allergy and intolerance	7 (14.3)	11 (11.2)	1.34	0.47, 3.84	NS
	Drug allergy‡	3 (6.1)	4 (4.1)	1.82	0.28, 11.95	NS
	Drug reaction	28 (57.1)	20 (20.4)	4.27	1.78, 10.23	<0.001
Non-IgE mediated	Contact dermatitis (nickel)	14 (28.6)	41 (41.8)	0.61	0.29, 1.27	NS
	Contact dermatitis (make up)	4 (8.2)	10 (10.2)	0.73	0.23, 2.28	NS

* Skin allergy: non-physical urticaria, contact dermatitis excluded. † Food allergy: urticaria after food ingestion (See Discussion). ‡ Drug allergy: urticaria, angioedema, and anaphylaxis only compared with drug reaction that includes any reported adverse reaction.

Table 3 Prevalence of atopy in SLE patients and controls: comparison of historical data alone with data supported by skin prick tests

	Positive history (%)	*Positive skin prick tests (%)*
Asthma		
SLE patients	6 (12.2)	4 (8.2)
Controls	13 (13.3)	8 (8.2)
Eczema		
SLE patients	4 (8.2)	4 (8.2)
Controls	10 (10.2)	6 (6.1)
Hayfever		
SLE patients	13 (26.5)	6 (12.2)
Controls	21 (21.4)	13 (13.3)
Allergic rhinitis		
SLE patients	15 (30.6)	8 (16.3)
Controls	27 (27.6)	14 (14.3)

they were not found to be at increased risk of urticaria, angio-oedema or anaphylaxis (OR 1.82, 95% CI 0.28, 11.95, p = 0.53). Table 2 shows that the frequencies of food allergy, insect allergy, skin allergy, and atopy were remarkably similar in cases and controls.

The value of SPT in confirming IgE mediated atopy is illustrated in table 3. It shows that reliance upon historical data alone would have resulted in over-reporting of the prevalence of asthma, hayfever, and allergic rhinitis.

Discussion

We have shown that the prevalence of symptoms of proven IgE and probable non-IgE mediated allergic problems in patients with SLE, is similar to that of the general population, which contrasts with previous data.[1 5–9 11] Forty nine per cent of SLE cases and 51% of healthy age and sex matched controls gave a history of allergy (OR 0.92, 95% CI 0.45, 1.86).

Our method of data collection compares favourably with others, in particular the effect of age, sex, and location on prevalence of allergy was taken into account when subjects were recruited. Age matching is required as the incidence of atopy tends to decrease with age[14] and sex matching was undertaken in view of the male predominance of asthma and hayfever in certain age groups.[14] The impact of exposure to air pollutants on prevalence of asthma and hayfever is still debated but there is mounting evidence from both laboratory and epidemiological studies that components of diesel exhaust fumes result in greater rates of sensitisation to aero-allergens such as pollen.[15] Our cases and controls were therefore recruited from both urban and rural areas.

We found no difference in prevalence rates of IgE mediated (skin prick test positive) and IgE associated atopic disorders in patients with SLE compared with controls. The percentage of cases and controls with asthma was identical as was the proportion of SLE patients and controls with atopic eczema. The prevalence of skin prick test positive hayfever in our SLE group (12.2%) was remarkably similar to that of the control group (13.3%, OR 0.9, 95% CI 0.31, 2.67, p=0.85) and there was no significant difference in numbers of patients and controls with skin prick test positive allergic rhinitis (16.3% and 14.3% respectively, OR 1.38, 95%CI 0.53, 3.57). These figures compare well with rates of atopy described in epidemiological studies of the general population. Nathan *et al* reported that 8.2% of their cohort had hayfever and that 14.2% had allergic rhinitis.[16] Atopic eczema has been described in 10.7% of 1 year old infants[17] and asthma in 10% of school children.[18] We did not confirm the association between SLE and atopy that Elkayam,[1] Goldman,[5] and Shahar[6] described but SPT was not used in these studies and Goldman acknowledged the difficulty distinguishing between "infectious, vasomotor and allergic rhinitis" from historical data alone.

Studies of drug allergy in lupus have led to considerable confusion as some authors have reported similar rates of drug allergy in SLE cases and controls, 26% compared with 20%[11] and others significant increases in SLE cases, 10% compared with 4%.[1] Some of the conflict has probably arisen through use of differing definitions, for example Petri and Allbritton[4] categorised rashes, hives, angio-oedema, fever, and wheezing as drug allergy and gastrointestinal upset as intolerance whereas we adopted the definition of Sequeira *et al*[8] that limits drug allergy to urticaria, angio-oedema, and anaphylaxis. The problem with including rashes, fever, and wheeze in definite drug allergy is that it can be difficult to distinguish between drug related reactions, those caused by infections for which the drugs were originally prescribed and the underlying lupus. Our finding of a fourfold increased risk of "drug reaction" in patients with SLE compared with healthy controls is not surprising and is probably, at least in part, a consequence of non-matching of cases with controls in terms of drug exposure. We found no significant difference in numbers of SLE cases and controls who had suffered presumed

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drug induced urticaria, angio-oedema or anaphylaxis.

Food allergy can be difficult to diagnose and requires confirmation with double blind placebo controlled food challenge.[19] Furthermore, frequently cases of patient reported food "allergy" actually represent intolerance.[20] The findings of our study reflect this observation, indeed, none of the reported reactions to food could definitely be attributed to Type 1 hypersensitivity, even the food associated urticaria that has nominally been referred to as "allergy" may in fact represent intolerance. An analysis of all types of food reaction did not yield any significant difference between patients with SLE and our healthy controls. Sequeira *et al* reported rates of food allergy of 9% in cases and 6% in controls (difference NS).[8] We are not however provided with details of the foods involved, or of the type of reaction reported by the patient—that is, urticaria, angioedema or anaphylaxis.

In people who had been stung by either a bee or wasp there was no difference in reports of severe, localised swelling (11.1% *v* 14.5%, OR 0.5, CI 0.06, 4.47). None of the subjects described generalised urticaria, angio-oedema or anaphylaxis. The reason for the significantly higher rates of insect allergy observed in people with SLE in the study by Sequeira[8] is not clear but measurement of venom specific IgE (not carried out here or by Sequeira) might help to resolve the issue in any future study.

Skin allergy was defined by Sequiera *et al* as "any urticarial or erythematovesicular skin reacions directly related to skin contact with allergens"—that is, contact dermatitis that is caused, either by a direct irritant effect or by a cell mediated immune mechanism. We however, included only urticaria under the heading of skin allergy as it is often IgE mediated. SLE cases were more likely to report urticaria than controls (OR 2.842, 95% CI 0.88, 4.69) although the difference did not reach statistical significance. When physical urticaria (heat and solar induced) was excluded from the equation the OR fell to 1.16 suggesting that the higher rates of urticaria observed in SLE are a reflection of photosensitivity.

In conclusion, we have shown that people with SLE are not at a clinically significant risk of IgE mediated/associated allergic disorders. It is therefore inappropriate to hypothesise that IgE mediated mechanisms are likely to be involved in the immunopathogenesis of SLE, or that SLE and allergy are related through a shared "TH2" response. We would add, however, that our study had limited power to rule out odds ratios of 2 or less, and to detect any low level of association larger sample sizes, for example, 400 SLE cases, would be required.

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