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Lupus 2010 19: 1614 originally published online 11 October 2010
DOI: 10.1177/0961203310379870

Lupus (2010) 19, 1614–1622
http://lup.sagepub.com

PAPER

Total serum IgE levels in systemic lupus erythematosus and associations with childhood onset allergies

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Elevated serum IgE has been described in systemic lupus erythematosus (SLE), but associations with disease risk and characteristics remain unresolved. We assessed total serum IgE levels and atopy (IgE > 100 IU/ml) in recently diagnosed SLE patients ($n = 228$) compared with population controls ($n = 293$) and in relation to disease activity, autoantibodies, clinical features, total immunoglobulins, C-reactive protein, and allergy history. Multivariate models estimated determinants of IgE and atopy in patients and controls, and associations of SLE with allergy and atopy. Total IgE levels were higher in patients than controls (median = 42 vs. 29 IU/ml); 32% of patients and 25% of controls were atopic ($p = 0.06$). IgE levels were significantly higher in non-Whites and patients reporting childhood onset (<18 years) asthma and hives, and in controls reporting childhood asthma, hay fever, eczema, and adult onset hives. After accounting for racial differences, atopy was not associated with SLE, nephritis, or other clinical and laboratory parameters. In sum, our findings provide limited evidence of a direct association between total serum IgE and SLE overall or with other disease characteristics after adjusting for demographic characteristics and allergy history. Future studies may want to explore potentially shared risk factors for development of allergy, atopy, and SLE. *Lupus* (2010) **19,** 1614–1622.

Key words: allergy; atopy; autoantibodies; autoimmunity; hygiene hypothesis; immunoglobulins; nephritis; population-based; systemic lupus erythematosus

Introduction

We recently described an inverse association of childhood farm exposure to animals and grains with systemic lupus erythematosus (SLE), suggesting the possible operation of the hygiene hypothesis.[1] The hygiene hypothesis initially stemmed from observational studies suggesting early-life infectious or microbial exposures may protect against development of asthma and allergy.[2] The hygiene hypothesis has also been invoked suggesting a similar protective effect of early microbial exposures on autoimmune diseases, and as a potential explanation for increased occurrence of autoimmune diseases in developed countries.[3,4] Although the relationship of allergic hypersensitivity and SLE has been infrequently examined, some studies show an association between SLE and allergic diseases, including hay fever, asthma, hives, and drug allergies.[5–9]

Elevated total serum IgE, sometimes considered a measure of clinical atopy, has also been described in SLE patients.[6,10–13] Some studies suggest that elevated IgE correlates with disease activity and nephritis,[13–15] but the relationship with allergy symptoms and diagnoses in SLE patients has been infrequently considered and findings have been inconsistent.[12,13] Previous studies examining determinants of IgE levels in SLE patients have been limited in the number of patients examined and in comparisons with controls, thus their findings are inconclusive. Still, these potential associations of SLE with atopy are intriguing, as they suggest the potential for common underlying risk factors or shared mechanisms of allergic and autoimmune phenotype.

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Received 21 September 2009; accepted 7 June 2010

10.1177/0961203310379870

In addition to our recent findings of an inverse association of SLE with childhood farm exposure to animals and grains,[1] previous analyses in the same study sample also suggested a modest relationship of SLE with history of some allergic diseases, e.g. asthma and hives.[5] Although overall allergy and asthma history did not appear to explain the observed protective effect of farm animal and grain exposures on SLE, we sought to better understand the determinants and correlates of allergic disease and risk of SLE in this population. In the present study, we measured total serum IgE levels and examined determinants of elevated IgE in the same sample of patients and population controls, considering demographic factors and self-reported history of allergic diseases. We also examined IgE in relation to SLE patient characteristics (disease activity, nephritis, autoantibodies) and other immunoglobulins and C-reactive protein levels in both patients and controls. Finally, we explored the association of atopic phenotype and allergic disease history comparing SLE patients with controls.

Methods

Study sample

Sample selection and enrollment in this retrospective case-control study has been described previously.[16] In brief, cases ($n = 265$) were recently diagnosed SLE patients from North and South Carolina, and met ACR criteria for definite SLE. Most (93%) referred cases were enrolled; 90% were female and 60% were African-American. Median time from diagnosis to study interview was 13 months and 75% of cases completed an in-person interview within 1.7 years of diagnosis. Controls ($n = 355$) were randomly selected from driver's license registries limited to the geographic region from which cases were identified, and frequency-matched on state, sex, and five-year age group. Of those controls screened and eligible, 75% enrolled. Controls were not matched to cases on race to empower both estimates of the effect of race on SLE and race-stratified analyses; 30% were African-American, similar to census estimates in the study population. The study protocol was approved by the review boards of all participating institutions.

Measurement of immunoglobulins and C-reactive protein

Blood specimens were obtained from 92% ($n = 244$) of cases and 85% ($n = 302$) of controls.[5,17] All assays were conducted on sera collected at study enrollment and stored at -70°C. Total serum IgE levels were measured using an Immulite 2000 (Siemens) on sera available at the time the present study was conducted, and assay results were available on 228 SLE patients and 293 controls. Other total immunoglobulin levels (IgG/A/M) were determined using a multiplexed microsphere kit (Beadlyte® Human IgG, IgA, IgM Kit, Millipore) on the remaining available sera on a subset of the study sample, 83 patients and 168 controls. High sensitivity C-reactive protein levels were evaluated as previously described.[18]

Questionnaire data on allergies and covariates

Data on self-reported history of allergy were based on responses to questions during an in-person interview, and included the occurrence and age of onset of hay fever and hives, physician diagnosed asthma and eczema, and allergic reactions to foods, medications, or insects (bees or wasps), defined as a reaction causing a rash or breathing difficulties, and not a reaction limited to stomach symptoms.[5] For the purpose of the present study, allergic disease history was defined as either childhood (<18 years of age) or adult onset. Self-reported allergies were categorized as 'probably IgE-mediated', including classical clinical allergies, i.e. hay fever, eczema, asthma, or 'possibly IgE-mediated or other', including hives (a potential indicator of systemic IgE-related hypersensitive responses to a variety of environmental allergens, including food, medication, or insects),[19] food, insect, or medication allergies, which can also be characterized by non-IgE mediated allergic mechanisms or as non-allergic symptoms, such as food intolerances.[20–22]. Because the present study considered indicators of both past and present allergic phenotype, we included all reported allergies up to the date of interview.

Covariates also collected by questionnaire included age, sex, state, self-reported race (parameterized as White and non-White, including primarily African-American, but also Native-American, Asian/Pacific Islander, Hispanic and other), and highest education level attained (less than high school, high school, some college or technical school, and college graduate or higher education).

SLE features and autoantibodies

Clinical features of SLE were obtained by medical records review, and data considered in the present analyses included factors contributing to the

ACR-criteria for lupus.[16] Specific autoantibodies were determined on patient sera at study enrollment as previously described.[16] Biopsy-based evidence of nephritis was determined through medical records review. Self-reported disease activity was based on two questions obtained by interview: (1) "Since you were first sick, has your disease been relatively constant or characterized by periods of flares and remission?"; if flares/remission (2), "Are you currently having a flare-up, or are you in remission?" Active disease was defined as those reporting their disease as being constant or in a current flare.

Analyses

Analyses were conducted in SAS (Version 9.1, Cary, NC, USA), and were limited to subjects with total IgE values (228 patients, 293 controls) or the subset with total IgG/A/M levels (83 patients, 168 controls). Descriptive frequencies were generated for demographics, allergy history, and patient characteristics. Distributions of IgE, C-reactive protein, and immunoglobulin levels were generated for patients and controls, and log-transformed means were compared.

Linear and logistic regression models were used to estimate associations for determinants of log-transformed IgE levels and atopy (IgE > 100 IU/ml) in parallel analyses for patients and controls, including demographic factors (age, sex, race, education), self-reported allergic disease history, and laboratory parameters (other immunoglobulins and C-reactive protein). We also examined IgE and atopy in relation to self-reported SLE activity and patient characteristics, including autoantibodies, nephritis and other clinical features. We performed stepwise comparisons of confounding by covariates, but no formal testing criteria were applied and all final models included age (continuous), sex, state (North Carolina/South Carolina), race (White, non-White), and education (four levels). Logistic regression was then used to estimate associations of atopy, and childhood and adult allergy with SLE in a mutually adjusted model including the same covariates. Additional models were run to examine confounding by levels of IgG/A/M in the subset with available data.

We also conducted exploratory analyses to consider potential differences in the association of atopy with probable IgE-related allergies and hives (functionally grouped based on associations with IgE levels in our data), in models stratified by demographic factors (race, age, and education) known to be associated with SLE or thought to be related to differences in allergic disease history or reporting. Lastly, we explored associations of these self-reported allergic diseases and SLE stratified by current atopic status. As these stratified analyses were conducted for descriptive purposes, no statistical testing of interactions was conducted.

Table 1 Characteristics of patients and controls: self-reported allergy history, clinical features and autoantibodies

	SLE patients N = *228* N *(%)*	*Controls* N = *293* N *(%)*
Demographics		
Age (years)		
15–29	69 (30)	78 (26)
30–38	57 (25)	70 (24)
39–50	49 (21)	71 (24)
>50	53 (23)	74 (25)
Female sex	204 (89)	266 (91)
Non-White race	144 (63)	92 (31)
Education		
<High school	46 (20)	28 (9)
High school	57 (25)	62 (21)
Some college	73 (32)	110 (38)
College graduate	52 (23)	93 (32)
Self-reported allergy history		
Probable IgE-mediated:		
Hay fever		
Childhood onset[a]	36 (16)	42 (14)
Adult onset	26 (11)	36 (12)
Eczema		
Childhood onset	8 (3)	9 (3)
Adult onset	10 (4)	15 (5)
Asthma		
Childhood onset	20 (9)	16 (5)
Adult onset	16 (7)	13 (4)
Possible IgE-mediated/other:		
Hives		
Childhood onset	29 (13)	27 (9)
Adult onset	37 (16)	35 (12)
Food allergies		
Childhood onset	15 (7)	21 (7)
Adult onset	29 (13)	17 (6)
Insect allergies		
Childhood onset	22 (10)	31 (11)
Adult onset	19 (8)	19 (6)
Medication allergies (any)	119 (45)	96 (27)
Clinical features and autoantibodies		
Currently active disease	127 (55)	NA
Biopsy proven nephritis	56 (25)	NA
Anti-SSA	77 (34)	NA
Anti-SSB	18 (8)	NA
Anti-Sm	27 (12)	NA
Anti-dsDNA	57 (26)	NA
Anti-RNP	60 (27)	NA

[a]Onset before age 18 years.

Results

Table 1 shows characteristics of SLE patients and population controls. The most commonly reported allergies were hay fever and asthma, with slightly more than half reporting childhood onset. Overall 32% of patients and 25% of controls reported at least one childhood onset allergy. Of the patients, 55% reported currently active disease and 25% had documented nephritis. IgE levels and other laboratory values are shown in Table 2. Mean total IgE levels were significantly higher in SLE patients than in controls, but values were skewed and showed less significant differences for comparisons of log-transformed means and atopy. Mean C-reactive protein levels were significantly higher in patients than controls, as were other immunoglobulin levels in the subset examined.

Table 3 shows results of unadjusted and adjusted models estimating the determinants of log-transformed IgE levels in patients and controls. After adjusting for covariates, higher IgE levels were significantly associated with non-White race and male sex in SLE patients, with a similar trend in controls. In both patients and controls, IgE levels were significantly elevated in those reporting childhood onset of asthma. In patients, IgE levels were significantly associated with history of childhood onset hives, while in controls IgE levels were also associated with childhood onset hay fever, eczema, and adult onset hives. Adult onset allergies and food, insect, or medication allergies were not associated with IgE levels in SLE patients.

Table 3 also shows IgE levels in relation to other laboratory measures and patient characteristics. Total IgE levels were not significantly associated with C-reactive protein levels in either patients or controls. Higher IgE levels were not associated with other immunoglobulin levels in patients after adjusting for race, but were significantly associated with higher IgG levels in controls. In patients, IgE levels were significantly associated with nephritis in the unadjusted model, but this association was substantially attenuated and no longer significant after adjusting for race. IgE levels appeared unrelated to self-reported disease activity, or other clinical features (not shown in table). With the exception of an inverse association with anti-RNP in the adjusted model, prevalence of specific autoantibodies was not associated with elevated IgE levels.

The associations between prevalent atopy (a dichotomous variable indicating elevated IgE) and allergic disease history followed a similar pattern to linear associations with continuous IgE levels (Table 4): in patients, atopy was significantly associated with selected childhood-onset allergies (adjusted odds ratio (Adj.OR) = 2.1, 95% confidence interval (CI) 1.1, 4.0), while in controls atopy was associated with both childhood (Adj.OR = 2.2, 95% CI 1.2, 4.2) and adult onset allergies (Adj.OR = 2.5, 95% CI 1.3, 4.5). Exploratory stratified models suggested potential racial differences in the association of childhood allergies and atopy in SLE patients, though confidence intervals were wide and overlapping due to the smaller number of White patients. There was little indication of differences in this association by years of education or age (not shown).

In an overall model including atopy, childhood, and adult-onset allergies, only childhood allergy was significantly associated with SLE risk (Adj.OR = 2.1; 95% CI 1.4, 3.3). Table 5 shows the association of allergy history with SLE, depending on current atopic phenotype. Childhood onset allergies remained significantly associated with SLE in both atopics and non-atopics. Adult onset allergy was associated with SLE only in non-atopic participants.

Table 2 Immunoglobulin and C-reactive protein levels in SLE patients and controls

	SLE patients N = *228*	*Controls* N = *293*	*p-value*[a]
Total IgE (IU/ml)			
Mean (95% CI)	238 (115, 361)	121 (85, 158)	0.045
Median (Q1, Q3)	43 (14, 134)	29 (11, 97)	
Range	1–9821	1–3394	
Atopic[b] *N* (%)	73 (32%)	72 (25%)	0.06
C-reactive protein[c]			
Mean, μg/ml (95% CI)	8.4 (7.3, 9.4)	6.7 (5.8, 7.5)	0.02
Other immunoglobulins	*SLE patients* *N* = 83	*Controls* *N* = 168	
Total IgG			
Mean mg/ml (95% CI)	16.6 (13.9, 19.2)	11.1 (10.5, 11.6)	<0.0001
Total IgA			
Mean mg/ml (95% CI)	0.79 (0.68, 0.90)	0.62 (0.58, 0.67)	0.01
Total IgM			
Mean mg/ml (95% CI)	0.88 (0.77, 0.99)	0.98 (0.91, 1.1)	0.02

[a]Comparing log-transformed mean immunoglobulin and C-reactive protein values, and difference in percent atopy, not adjusted for demographics.
[b]IgE above 100 IU/ml.
[c]hs-C-reactive protein levels, missing in one case ($n = 227$).

Discussion

Although previous clinical studies suggested a possible elevation of total serum IgE levels in SLE

Table 3 Determinants of total IgE levels in SLE patients and population controls

	SLE patients N = *228* *Unadjusted beta* (p-*value*)	*Adjusted*[a] *beta* (p-*value*)	*Controls* N = *293* *Unadjusted beta* (p-*value*)	*Adjusted*[a] *beta* (p-*value*)
Demographics				
Age (years)				
15–29	Referent	Referent	Referent	Referent
30–38	−0.03 (0.93)	−0.07 (0.80)	−0.37 (0.15)	−0.34 (0.18)
39–50	**−0.63 (0.04)**	−0.59 (0.06)	−0.10 (0.71)	−0.11 (0.67)
>50	**1.28 (0.03)**	**1.38 (0.02)**	0.11 (0.80)	0.02 (0.97)
Female sex	**−0.85 (0.02)**	**−0.97 (0.009)**	−0.53 (0.09)	−0.58 (0.06)
Non-White race	**0.52 (0.02)**	**0.75 (0.002)**	**0.40 (0.04)**	0.33 (0.10)
Education				
<High school	−0.37 (0.27)	−0.58 (0.09)	**1.05 (0.002)**	**0.90 (0.008)**
High school	−0.28 (0.38)	−0.72 (0.31)	0.10 (0.70)	0.02 (0.91)
Some college	−0.19 (0.52)	−0.17 (0.56)	0.08 (0.70)	0.05 (0.82)
College graduate	Referent	Referent	Referent	Referent
Self-reported allergy history				
Probable IgE-mediated:				
Hay fever				
Childhood onset[b]	0.13 (0.66)	0.17 (0.57)	**0.86 (0.001)**	**0.99 (0.001)**
Adult onset	0.03 (0.94)	−0.03 (0.92)	0.47 (0.08)	0.50 (0.07)
Eczema				
Childhood onset	0.39 (0.52)	0.10 (0.86)	**1.06 (0.04)**	0.97 (0.06)
Adult onset	0.30 (0.58)	0.26 (0.63)	−0.40 (0.33)	−0.38 (0.36)
Asthma				
Childhood onset	**1.1 (0.006)**	**0.98 (0.011)**	**1.02 (0.01)**	**1.06 (0.008)**
Adult onset	−0.65 (0.14)	−0.74 (0.09)	0.55 (0.21)	0.49 (0.27)
Possible IgE-mediated/other:				
Hives				
Childhood onset	**0.66 (0.049)**	**0.68 (0.045)**	0.36 (0.25)	0.56 (0.07)
Adult onset	−0.21 (0.49)	−0.02 (0.75)	**0.57 (0.04)**	**0.67 (0.02)**
Food				
Childhood onset	0.85 (0.06)	0.70 (0.11)	0.38 (0.28)	0.33 (0.35)
Adult onset	−0.24 (0.47)	−0.38 (0.24)	0.58 (0.13)	0.49 (0.19)
Insects				
Childhood onset	−0.06 (0.87)	−0.26 (0.48)	−0.00 (1.0)	0.15 (0.60)
Adult onset	−0.05 (0.91)	0.07 (0.87)	0.44 (0.22)	0.54 (0.15)
Medications (any)	−0.23 (0.30)	−0.00 (0.99)	0.13 (0.52)	0.21 (0.30)
C-reactive protein	*N* = 227		*N* = 293	
lnCRP	0.03 (0.72)	0.002 (0.99)	0.10 (0.18)	0.09 (0.22)
Immunoglobulins	*N* = 83		*N* = 168	
ln(IgG)	0.61 (0.09)	0.36 (0.43)	**0.92 (0.02)**	**0.87 (0.047)**
ln(IgA)	**0.64 (0.04)**	0.51 (0.17)	0.44 (0.11)	0.39 (0.17)
ln(IgM)	−0.08 (0.79)	0.20 (0.50)	−0.33 (0.19)	−0.26 (0.34)
Clinical features and autoantibodies	*N* = 228			
Biopsy proven nephritis	**0.59 (0.009)**	0.28 (0.22)		
Currently active disease	−0.22 (0.32)	−0.12 (0.59)		
Autoantibodies:				
SSA	−0.15 (0.53)	−0.15 (0.53)		
SSB	−0.65 (0.11)	−0.63 (0.13)		
Sm	0.13 (0.70)	−0.13 (0.71)		
dsDNA	−0.13 (0.62)	−0.34 (0.20)		
RNP	−0.28 (0.27)	**−0.71 (0.01)**		

[a]Linear regression models: log-transformed IgE levels, Adjusted models included age, sex, state, race, and education; numbers in bold indicate statistically significant associations ($p < 0.05$).
[b]Any (one or more) allergy with childhood onset, before age 18 years.

Table 4 Association of atopy (total IgE > 100 IU/ml) with history of childhood and adult onset allergies SLE or hives patients and controls: overall and stratified by race

Probable IgE-mediated allergies or hives[a]	*Adjusted odds ratio*[b] *(95% confidence interval)*	
	SLE patients	*Controls*
Everyone		
Childhood onset	**2.1 (1.1, 4.0)**	**2.2 (1.2, 4.2)**
Adult onset	1.3 (0.69, 2.5)	**2.5 (1.3, 4.5)**
Whites		
Childhood onset	**8.4 (1.9, 36.9)**	**2.5 (1.1, 5.4)**
Adult onset	0.90 (0.26, 3.1)	**4.2 (1.9, 9.5)**
Non-Whites		
Childhood onset	1.1 (0.48, 2.5)	2.2 (0.55, 8.5)
Adult onset	1.6 (0.74, 3.5)	1.4 (0.35, 5.3)

[a]Onset in childhood (before age 18 years) or in adults (age 18 years or older) of probable IgE-mediated allergy or hives.
[b]Estimated by logistic regression adjusting for age, race, sex, state, education; referent: those with no reported probable IgE-mediated allergies, bold numbers: confidence interval excludes the null, $p < 0.05$.

Table 5 Association of allergy history with SLE, comparing patients with controls and stratified by current atopy

	Atopic OR (95% CI)[a]	*Non-atopic OR (95% CI)*[a]
Allergies[b]		
Childhood onset	**2.4 (1.0, 5.8)**	**2.3 (1.3, 3.9)**
Adult onset	0.82 (0.36, 1.9)	**1.7 (1.0, 2.8)**

[a]Odds ratios (OR) and 95% confidence intervals (CI) estimated by logistic regression adjusting for age, race, sex, state, education; bold numbers: CI excludes the null, $p < 0.05$.
[b]Probable IgE-mediated allergies or hives; childhood onset before age 18 years, adult onset age 18 years and older.

patients,[6,11–13] we observed that the apparently higher IgE levels in this sample of SLE patients compared with population controls were primarily related to demographic characteristics and history of self-reported allergies. Case phenotype, subjective, and laboratory indicators of disease activity were also unrelated to IgE levels after accounting for race, which contradicts the idea that IgE levels might be either causally or co-incidentally related to higher immunoglobulin levels and immunological activity in SLE patients. Rather, patient IgE levels and atopy were consistently associated with history of childhood onset asthma and hives. Taken together with evidence of an association between childhood onset allergies and SLE, these findings support further investigation of potentially shared underlying risk factors for allergy, atopy and SLE.

Confidence in our findings is increased by the replication of previously described associations, for example, higher total IgE levels in males and in non-Whites, with similar patterns seen in patients and controls. Our non-White population included primarily African-Americans (60% of cases, 30% of controls). Although the underlying reason for racial differences in IgE levels is unknown, prior studies have identified higher total IgE levels in African-Americans, who also tend to have more frequent sensitization to a variety of specific allergens.[23,24] Studies have also shown more severe asthma in African-Americans, though the reasons for this are not well understood.[25] One possible explanation of this pattern could be the well-documented racial difference in vitamin D levels,[26] considered as a potential risk factor for many diseases, including asthma and lupus.[27,28] Low vitamin D has been associated with elevated IgE levels, though the relationship may be non-linear or U-shaped.[29] In a previous sub-study of participants in the present sample, vitamin D levels were lower in African-Americans;[30] however, there was only limited evidence of an association between low vitamin D and higher IgE levels, with an inverse association among Black controls, but not in Black patients or in Whites (results not shown). Other exposures may be related to higher IgE levels, such as smoking or alcohol use.[31] Further studies may wish to investigate these and other environmental factors in relation to atopy and allergic phenotype in SLE.

Inconsistencies in our findings included the associations of IgE levels with age and education in patients compared with controls. Lower education was significantly associated with higher IgE levels and atopy in controls, but in patients an association of IgE and lower education was not observed. Socioeconomic factors may be associated with differences in SLE severity or use of immunosuppressive medications that have a broad influence on the immune system, and might have impacted current IgE levels. The elevation in IgE levels observed in older SLE patients was unexpected, and not seen in controls. This finding might reflect age-related differences in disease treatment, i.e. use of immunosuppressive medications may be less common in older patients.[32] We did not have medication data at enrollment and therefore could not directly address these questions. Our ability to address disease activity was limited to a subjective measure (self-report of whether disease was flaring) and laboratory indicators of inflammation and antibody levels. However, we saw no indication that IgE levels were independently associated with either

self-assessed disease activity or with measured high sensitivity C-reactive protein (hs-CRP) and other serological markers. Though the role of CRP in SLE is unresolved, hs-CRP levels were associated with standardized disease activity measures, SLAM, and elements of the SLICC Damage index, in the LUMINA cohort.[33]

Compared with other immunoglobulins, serum IgE levels are typically low and function by triggering acute inflammatory reactions as part of the normal immune response to helminth infection.[34] In allergic individuals, total IgE levels may reflect the potential for antigen-specific IgE production associated with hypersensitivity reactions. Studies of IgE-mediated allergies often utilize allergen-specific tests; however, elevations in total IgE may be correlated with allergen-specific IgE depending on past and recent environmental exposures.[35] Because of the hypothesis generating nature of the present analyses, we did not conduct allergen-specific serological testing. However, these results support further investigation of atopy in relation to SLE. Although the association of IgE levels with allergic phenotype is generally accepted, this is the first study to demonstrate an association with self-reported history of childhood onset allergies in SLE patients.

Allergy can be defined as any excessive immune response to environmental antigens (allergens), regardless of mechanism, whereas atopic allergies are those manifest by type I hypersensitivity, or IgE-mediated responses.[19] Determining allergic or atopic phenotype by questionnaire is difficult, as symptomatic allergies may vary in their site, frequency, and severity. Furthermore, while allergies may be triggered by exposure to various ubiquitous or episodic exposure to antigens, some may appear early in life while others manifest later in adulthood. For the purpose of these analyses, our functional definition of allergic history was based on a simple series of questions on allergic symptoms or diseases, including age at first appearance or diagnosis. We categorized self-reported allergies as those more likely to be mediated by allergen-specific IgE production: hay fever, asthma, and eczema,[19] and other possible IgE-mediated disorders. Hives may sometimes indicate systemic IgE-related responses to various allergens, including food, medication, or insects,[19] and in our data self-report of hives was related to elevated IgE levels in both cases and controls. Hives may also include chronic forms that are not IgE-related, but our questionnaire did not differentiate types of hives. Some kinds of food, insect, or medication allergies may also be IgE-mediated, but self-report of these allergies is likely to include other types of hypersensitivity or intolerances[20–22] and the available data did not enable us to identify possible atopic versus non-atopic reactions. History of transient or mild allergic symptoms is likely to be subject to inaccurate recall. Longitudinal studies suggest that self-report of past allergies may be fairly specific, though insensitive, and allergies with childhood onset may be better reported by those with severe disease or persisting symptoms in adulthood.[36,37] The consistent associations we observed between many of the self-reported allergies and total IgE levels in the present study increased our confidence in the data.

Another limitation of the present study is a lack of information on current or recent allergic symptoms. However, allergies typically persist after onset, with triggering of symptoms depending on allergen exposure. The vast majority of allergies were reported as occurring prior to the age of diagnosis or reference date in controls, though a small number (33 cases, 21 controls) reported onset within two years of diagnosis. We chose to differentiate allergic diseases by reported age at onset. Though the reasons underlying the differences in age at onset are not fully understood, earlier onset might be due to a variety of genetic, developmental, or early-life environmental factors. Onset of adulthood allergies may also reflect atopic 'march' or new workplace or environmental exposures.[19,38]

We undertook the present analyses to better understand the determinants and correlates of allergic disease and risk of SLE in this population, following up earlier findings suggesting potential operation of the hygiene hypothesis, showing that agricultural contact with livestock and grains was inversely associated with SLE. While this was the first such report in SLE, previous studies suggest early-life exposures to organic dusts or endotoxin (a component of gram-negative bacterial cell walls) may protect against allergic sensitization,[38] or childhood autoimmune disease.[39,40] The hygiene hypothesis generally posits that the timing and burden of microbial exposures may be related to susceptibility to developing aberrant immune reactivity to ubiquitous environmental antigens (e.g. allergy) or self-antigens (e.g. autoimmunity). Relatively few studies have directly examined the hygiene hypothesis in relation to autoimmune diseases such as SLE, which may be complicated by the potential role of infectious risk factors.[3,4] Several studies have indirectly considered this relationship by examining autoimmune diseases in relation to allergies and asthma; studies showing positive associations[41,42] have suggested that

shared risk factors may contribute to dysregulation of the immune response to common or intrinsic antigens. In addition to shared environmental factors, such as early-life microbial exposures or nutritional factors, autoimmune and allergic diseases may share genetic predisposition, for example polymorphisms in Secreted Phosphoprotein 1 gene associated with both higher total IgE levels and SLE[43,44] Other examples may include genes interacting with shared environmental risk factors, for example IL-10, which is involved in the vitamin D pathway and has been associated with both associated with asthma and lupus.[45–47]

In sum, this is the largest study to date describing IgE levels in SLE patients, including a systematic comparison with population-based controls. Though lacking data on current allergic symptoms or medication use, our findings provided no evidence of an independent association of IgE levels SLE and patient characteristics, such as self-reported disease activity, nephritis, C-reactive protein, or other immunoglobulin levels. Rather, IgE levels were consistently associated with history of childhood allergies, including asthma and hives, which were also associated with SLE. Taken together, these findings support investigation of environmental and genetic factors that might be related to childhood onset allergies and risk of SLE.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health or the Environmental Protection Agency.

Funding

This work was supported in part by the intramural research program of the NIH, National Institute of Environmental Health Sciences, by the National Institute for Occupational Safety and Health, and by an interagency agreement between NIOSH and National Institute of Environmental Health Sciences (NIEHS) (grant number Y1-ES-0001-Clinical Immunotoxicity).

Conflict of interest statement

None declared.

Acknowledgement

The authors appreciate the insightful comments of Lisa Rider and Jane Hoppin on earlier versions of the manuscript.

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