

Lack of correlation between titers of serum allergen-specific IgE and symptoms in untreated patients with seasonal allergic rhinitis

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In five ragweed seasons and three grass pollen seasons, preseason and postseason ragweed-specific serum IgE and nasal secretory-specific IgE and IgA have been measured in untreated patients with seasonal allergic rhinitis. There was no consistent correlation between severity of rhinitis, as measured by symptom/medication scores during the season, and either absolute or changes in antibody titers. These findings suggest that antibody levels are only one of the factors that determine symptom severity. (J ALLERGY CLIN IMMUNOL 77:43-8, 1986.)

It has been generally assumed that the severity of symptoms of allergic rhinitis in patients who are not receiving immunotherapy relates to immunologic reactivity as reflected by specific IgE antibody titers. During the past 5 years, we have measured preseason ragweed- and grass-specific IgE and nasal secretory ragweed- and grass-specific IgA in untreated allergic patients who have served as control subjects in local nasal immunotherapy studies. All patients kept symptom/medication records during the season, and in many, antibody titers were measured after pollen exposure. The results of these observations indicate no consistent correlation between antibody titers or changes in antibody titers and symptoms of grass and ragweed seasonal allergic rhinitis.

MATERIAL AND METHODS

Patient selection

Patients aged 16 years or more were selected on the basis of a typical history of allergic rhinitis during the ragweed or grass pollen season. All had positive prick skin test reactions to a 5% solution of grass or ragweed allergen. Skin tests also were performed with 5% extracts of *Alternaria*, *Cladosporium*, and mixed trees (elm, oak, poplar, and ma-

Abbreviation used

SMS: Symptom/medication scores

ple). Ragweed-sensitive patients were excluded if they reacted to either of the two mold extracts. Grass-sensitive patients were excluded if they had positive skin tests to the tree extracts. Patients also were excluded for the following criteria: perennial rhinitis, severe asthma, use of steroids, or nasal congestant sprays.

These patients served as control subjects for the studies of local nasal immunotherapy. They were assigned, usually randomly, to the control group and received either an intranasal histamine-placebo spray, varying from 0.05 to 5 mg/ml, or received no placebo treatment. The ragweed studies were done each year from 1979 through 1983,¹⁻⁵ and the grass studies were done from 1981 through 1983.⁶⁻⁸ The number of patients in each study is illustrated in Table I.

SMS

Symptom/medication diaries were kept by each patient during the appropriate pollen season.⁹ Sneezing, rhinorrhea, congestion, eye symptoms, and the overall assessment of disease were graded for severity and duration. The number of antihistamine tablets taken during each 12-hour period also was recorded. A daily SMS was computed from the diaries. Each patient's mean SMS was determined by averaging the daily SMS over the peak pollen season. The peak pollen season was defined as the period of consecutive days with pollen counts >30 gr/mm³ of ragweed and >20 gr/mm³ of grass. Pollen counts were determined daily by the rotorod method (Ted Brown Associates, Los Altos, Calif.).

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TABLE I. Summary of patient SMS and antibody titers in the five ragweed and three grass season studies

Study	No. patients	SMS	Serum* allergen-specific IgE		Nasal secretory allergen-specific IgE		Nasal secretory† allergen-specific IgA	
			Preseason	Postseason	Preseason	Postseason	Preseason	Postseason
Ragweed								
1979	21	3.94‡ (0.56 to 8.73)‡	49 (8 to 384)	71§ (9 to 468)	2.8 (1 to 10)	6.0 (3 to 34)	7.40 (1 to 60)	5.6 (0 to 16)
1980	14	4.62 (1.31 to 7.47)	44 (6 to 275)	73 (9 to 440)	15.7 (0 to 105)	7.0 (0 to 22)	4.6 (0.5 to 8.3)	6.0 (2.2 to 10.2)
1981	18	2.04 (0 to 4.58)	8 (0 to 120)	ND	ND	ND	3.8 (1.6 to 7.9)	ND
1982	25	4.36 (1.93 to 6.43)	17 (0 to 200)	ND	ND	ND	ND	ND
1983	12	3.93 (0.64 to 8.69)	22 (3 to 255)	44 (4 to 1000)	ND	ND	6.8 (3.3 to 14.2)	6.7 (2 to 13.5)
Grass								
1981	13	2.79 (1.35 to 5.34)	9 (0 to 57)	19 (0 to 120)	2.3 (0 to 5)	3.7 (0 to 10)	3.6 (1.3 to 7.2)	3.7 (1.2 to 9.3)
1982	16	3.24 (0.97 to 7.75)	13 (1 to 430)	10 (1 to 98)	ND	ND	3.1 (0.8 to 4.8)	3.4 (1.1 to 6.5)
1983	12	2.57 (0.53 to 5.03)	8 (1 to 1100)	17 (1 to 1300)	ND	ND	2.6 (1.7 to 4.6)	2.8 (1.3 to 6.4)

ND = not done.

*IgE antibodies expressed as percent of a positive standard.

†SIgA antibodies expressed as net percent binding.

‡Mean (range). Statistically significant changes in antibody titers: § $p < 0.01$; || $p < 0.001$.

Antibody determinations

Sera and nasal secretions were collected just before the pollen season and after the pollen season. Nasal secretions were obtained during a paper-disc antigen nasal challenge with the same allergen to which the patient was sensitive, either mixed grass or mixed ragweed extracts.¹⁰ Application of allergen does not affect antibody titers in secretions. Similar titers have been found after challenges with allergen and histamine (unpublished data). Secretions were collected by having the patients blow onto Para-film (American Can Co., Greenwich, Conn.). The preseason and postseason samples were stored at -20°C and were analyzed simultaneously. Antibody determinations were done on the sera and the liquid phase of the undiluted secretions by use of the paper-disc radioimmunoassay as described previously.² Briefly, preliminary experiments were done each year to determine the optimal amount of grass and ragweed pollen extracts for coupling to CNBr-activated discs. The same extracts used for treatment were used in the RAST. Twenty-five to 250 μg of ragweed or grass extract were coupled to each disc. Results of serum and nasal secretory grass- and ragweed-specific IgE were expressed in percent of net binding of the serum pool from ragweed-sensitive patients to ragweed discs. A net binding of $>5\%$ of the positive standard was considered significant. Nasal secre-

tory grass- and ragweed-specific IgA was reported as net percent of total bound radioactivity, since a positive standard was not available. Duplicate determinations agreed within 10%.

Statistical methods

Nonparametric methods were used in analysis involving the SMS.¹¹ Correlations between antibody levels and SMS were done by use of the Spearman rank-sum coefficient. The paired t test was used for comparisons between pre-seasonal and postseasonal antibody levels. Serum IgE levels were transformed to their log values for analysis. Secretory antibody levels were normally distributed and were not transformed to log values.

RESULTS

The preseason and postseason antibody levels and SMS for each study are illustrated in Table I.

Fig. 1 illustrates the preseason ragweed-specific IgE titers and SMS for patients in all five ragweed studies. There was a statistically significant correlation in only two of the years (Table II: $r = +0.53$, $p < 0.02$, 1981; $r = +0.46$, $p < 0.05$, 1982). The correlation coefficient was negative in two of the other three

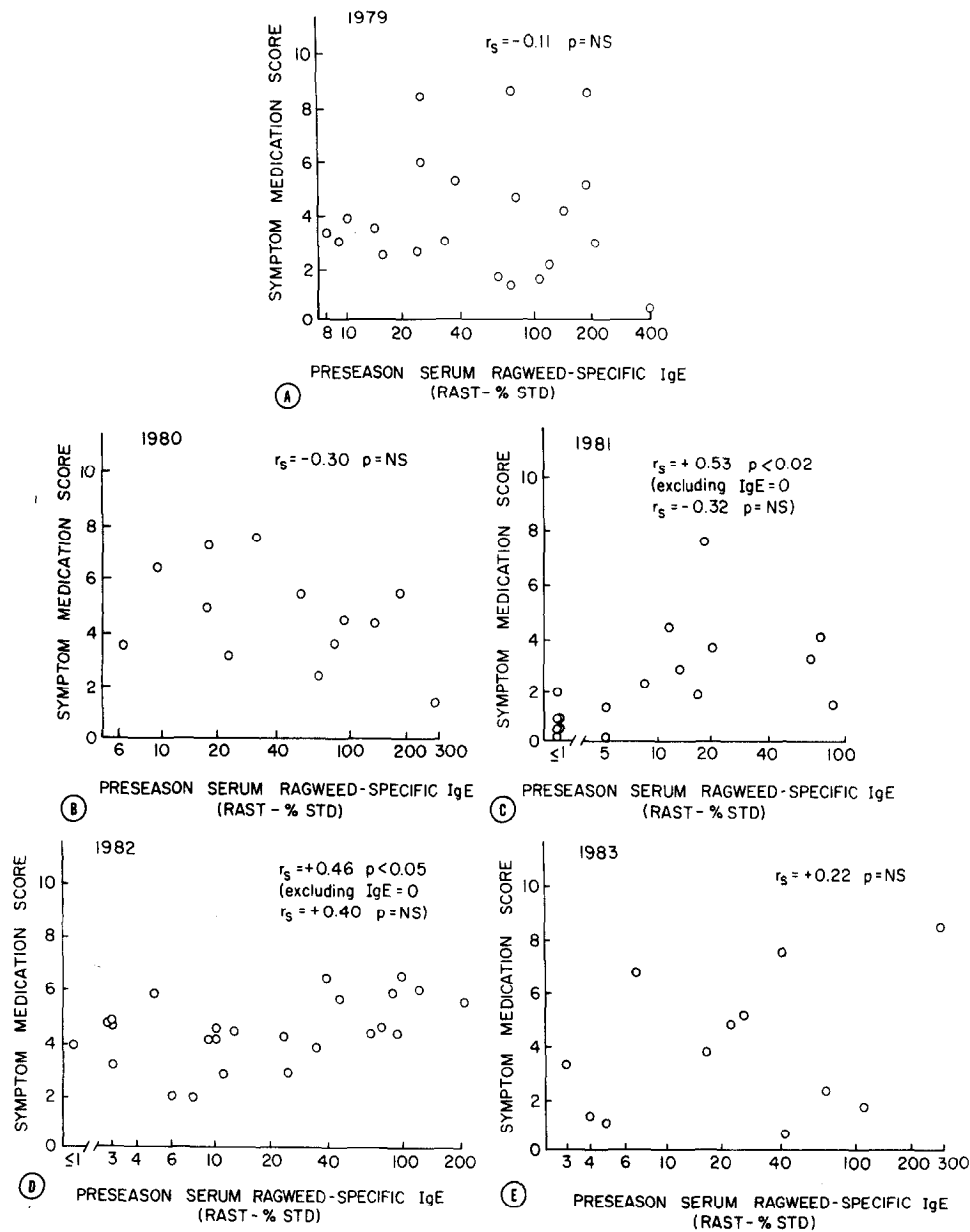


FIG 1, A-E. Correlations between SMS during the 1979 to 1983 ragweed pollen seasons and preseason serum ragweed-specific IgE expressed as percent of a positive standard.

years. After ragweed pollen exposure, serum ragweed-specific IgE increased in almost every patient. The mean increase was statistically significant in each season; however, there was no correlation between the change in titer and SMS. Nasal secretory ragweed-specific IgE and IgA did not change in any systematic way.

The results of the grass studies are presented in Fig. 2. There was no significant correlation between preseason serum grass-specific IgE and symptoms in any of the three grass studies. The correlation between the nasal secretory allergen-specific IgE and IgA antibody

levels and SMS is illustrated in Table II. There was no significant correlation in any of the studies.

Data were reanalyzed, excluding subjects with preseason allergen-specific IgE levels of zero (Table II). When these patients were excluded, there was no statistically significant correlation between the serum grass- or ragweed-specific IgE titers and SMS in any of the study years, and, in fact, the 1981 ragweed study now had a negative correlation. Correlations also were examined in a subset of patients with preseason serum allergen-specific IgE levels of >10 . With this selection criteria, the only statistically sig-

TABLE II. Summary of correlations between patient SMS and antibody titers

Study	Serum allergen-specific IgE						Nasal secretory allergen-specific IgE		Nasal secretory allergen-specific IgA	
	All patients		Preseason titers >0		Preseason titers >10		N	r	N	r
	N	r	N	r	N	r				
Ragweed										
1979	21	-0.11		No change	19	-0.13	19	+0.43	21	+0.14
1980	14	-0.30		No change	12	-0.39	13	-0.52	14	-0.33
1981	18	+0.53	12	-0.32	9	-0.54	ND		16	-0.44
		$p < 0.02$								
1982	25	+0.46	24	+0.40	16	+0.54	ND		ND	
		$p < 0.05$				$p < 0.02$				
1983	12	+0.22		No change	8	-0.02	ND		11	+0.15
Grass										
1981	13	+0.42	11	+0.10	7	-0.46	11	+0.41	12	-0.55
1982	16	+0.04		No change	9	0.00	ND		16	-0.13
1983	12	-0.07		No change	4	+0.40	ND		12	+0.03

ND = not done.

nificant correlation was found in the 1982 ragweed study.

DISCUSSION

Patients in the study were carefully selected. They had classic grass and ragweed pollenosis confirmed by positive skin test reactions. To avoid any effects of other airborne allergens present at the same time, ragweed-sensitive patients reacting to *Alternaria* or *Cladosporium* extracts and grass-sensitive patients reacting to tree extracts were excluded from the study.

Although there have been many control trials of various treatments for allergic diseases, there are surprisingly few studies that comment on the correlation of antibody levels to objective measurements of the severity of symptoms in untreated patients. In this study there was little correlation between ragweed- and grass-specific antibodies in serum or nasal secretions and symptoms during the pollen season. In only two of five ragweed seasons was there a significant correlation between symptoms and preseason ragweed-specific IgE titers.

After exclusion of less sensitive patients (RAST = 0), only the 1982 study demonstrated a continued positive correlation (0.40). In order to observe only a subset of patients with high sensitivity, data were reexamined for those patients with IgE antibody levels of >10. Only the 1982 ragweed study demonstrated a significant correlation. In the other four ragweed seasons and the three grass seasons, no correlations could be found.

Lichtenstein et al.¹² and Norman et al.¹³ examined

the association between IgE-mediated activity and the severity of symptoms in untreated ragweed-allergic patients and found a highly significant correlation between basophil histamine release and seasonal symptoms. In these studies serum IgE antibody levels did not correlate well with SMS when all the patients were analyzed. Analysis of a subset of patients who released >50% of the leukocyte histamine (high histamine releasers) did demonstrate a statistically significant correlation between serum IgE levels of this subset and seasonal symptoms in the first year of their study but not in the second year. End point skin test titration and seasonal symptoms also correlated in this subset of patients who were high histamine releasers but not in the group as a whole. The authors concluded that there was a relationship between ragweed-specific IgE levels and symptoms, but symptoms were dependent on other important factors, one of which was the releasability of histamine by sensitized basophils.

Freidhoff et al.¹⁴ reported on correlations between SMS, serum IgE titers, and allergy index derived from skin test results. They found that in a group of 22 allergic patients studied during 1 year, there was a weak correlation with the allergy index and SMS ($r = 0.2$ to 0.4) and no correlation with weekly SMS and log values for total IgE ($r = -0.03$ to -0.30); however, in 14 ragweed-allergic patients, these authors noted a moderate correlation between SMS and the allergy index for ragweed ($r = 0.59$, $p < 0.05$) and a good correlation between SMS and log values for serum ragweed-specific IgE ($r = 0.69$, $p < 0.01$). These subjects were selected from a large group

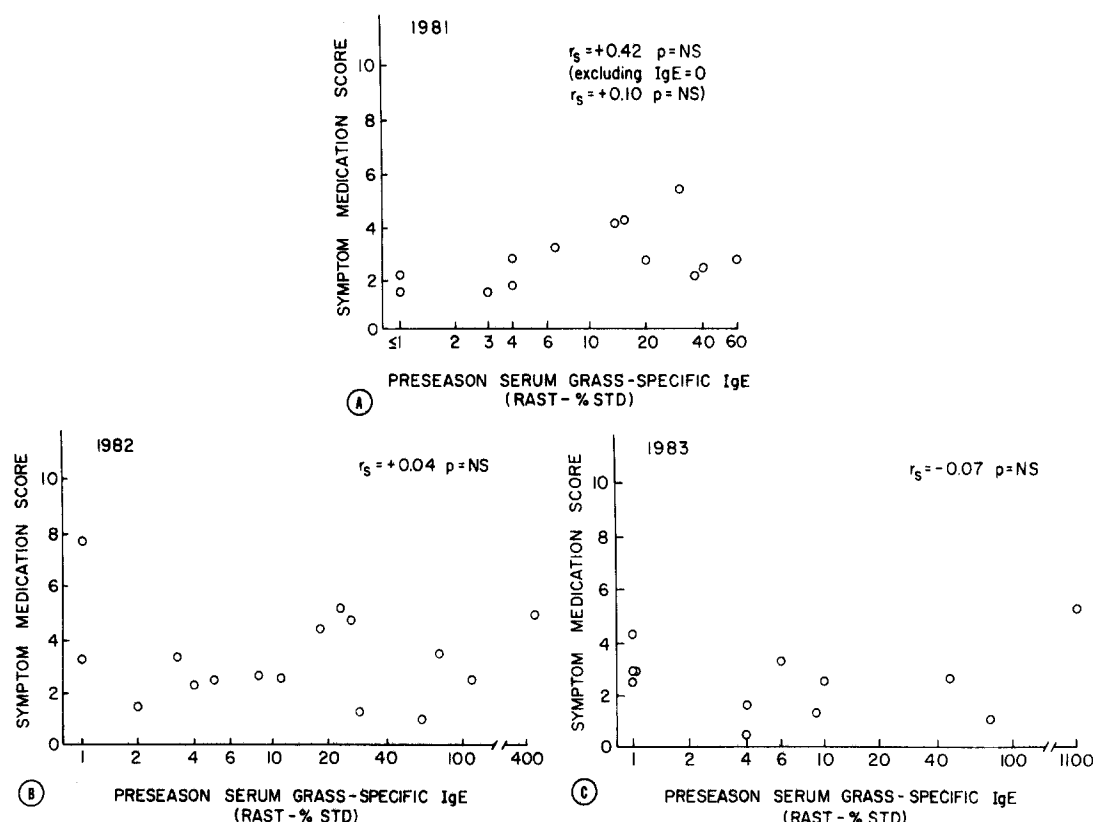


FIG. 2, A-C. Correlations between SMS during the 1981 to 1983 grass pollen seasons and pre-season grass-specific IgE expressed as percent of a positive standard.

of patients who had a positive skin test to ragweed, but no mention is made of any specific selection criteria.

Theoretically, nasal secretory antibody activity might be a better parameter of clinical reactivity. The SIgA antibody is produced locally and possibly could be a reflection of immunity. The IgE antibody detected in nasal secretions could be produced locally or result from transudation from serum and might influence sensitivity. In this study the antibody levels in nasal secretions were not a better predictor of SMS. There was no correlation between absolute antibody levels measured in nasal secretions and SMS. These findings are in agreement with the two other studies that examined the correlation between nasal secretory antibody levels and symptoms. Platts-Mills et al.¹⁵ quantitated both IgA and IgG blocking antibodies in nasal secretions of patients with ragweed rhinitis and were unable to demonstrate any correlation between antibody levels and SMS. Mathews et al.¹⁶ also found no significant correlation between antibody levels and symptoms in untreated patients or in patients treated with local nasal immunotherapy. Neither of these investigators examined nasal secretory IgE antibody levels.

Most control patients in this study had the expected

coseasonal increase in serum allergen-specific IgE. There was no correlation between the magnitude of this rise and SMS. In addition, there was no correlation between the magnitude of the change in nasal secretory antibodies and SMS.

These findings suggest that antibody levels are only one of the factors that determine symptom severity.

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Increased bronchial responsiveness to exercise and histamine after allergen challenge in children with asthma

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*Nonspecific bronchial reactivity to exercise and histamine was measured in nine children with asthma before and within nine days after allergen inhalation. All patients developed an immediate fall in FEV₁ of $\geq 16\%$ after allergen inhalation, and five children also developed a definite late asthmatic response with a fall in peak expiratory flow of $\geq 14\%$ after 3 to 8 hours. Mean postexercise fall in FEV₁ (Δ FEV₁) of the whole group was significantly greater after allergen challenge compared with that of control subjects ($29 \pm 6\%$ and $16 \pm 4\%$; $p = 0.013$). There was no change in refractoriness to repeated exercise after allergen challenge. The mean provocation concentration of histamine causing a decrease in FEV₁ of 20% of the whole group was less after allergen challenge compared with that of control subjects (0.47 ± 0.18 and 0.62 ± 0.13), but this was not statistically significant ($p = 0.19$). Of the five children with late allergen reactions, all demonstrated increased histamine sensitivity, and all four children who developed definite exercise-induced asthma also demonstrated increased sensitivity to exercise. Of the four children without late allergen reactions, none demonstrated increased histamine sensitivity, but two of the three children with definite exercise-induced asthma demonstrated increased sensitivity to exercise. It may be that sensitivity to exercise is more easily affected by nonspecific reactivity than sensitivity to histamine. It is concluded that increased bronchial responsiveness to both exercise and histamine occur after allergen provocation in patients with asthma. (*J ALLERGY CLIN IMMUNOL* 77:48-52, 1986.)*

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Nonspecific bronchial reactivity to histamine, methacholine, and exercise is characteristic of asthma.¹ In general there is a correlation between the responsiveness to histamine and exercise, but this is not always the case.² It has been observed that patients with asthma have increased nonspecific bronchial reactivity