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Atopy and IgE in patients with leprosy

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The atopic status of patients with leprosy was assessed by medical history, physical examination, serum total IgE, and specific IgE antibodies to common allergens (by skin testing and RAST). Tests for specific IgE antibody to Mycobacterium leprae were performed by RAST and immunoblotting technique. We studied 28 patients with leprosy and 49 control subjects. The two groups did not differ significantly in the prevalence of atopic disease. The IgE level was significantly higher in the patients, however, than in the control subjects, whether there was atopy (296.1 versus 96.3 IU/ml) or not atopy (72.9 versus 18.9 IU/ml). Neither RAST nor immunoblotting technique detected significant levels of IgE antibodies to M. leprae. Our data indicate that leprosy was associated with increased total IgE level, but clinical atopy in patients with leprosy was similar to that in control subjects. The observed IgE increase in patients with leprosy appears to be generally nonspecific. (J ALLERGY CLIN IMMUNOL 1990;85:795-800.)

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Abbreviations used

RIA: Radioimmunoassay

Gx: Geometric mean

Elevations in IgG, IgM, and IgA levels in association with leprosy have been reported.^{1,2} Serum total IgE level in patients with leprosy has been reported by some authors as normal^{3,4} and by other authors as

TABLE I. Characteristics and serum total IgE level in patients with leprosy and control subjects according to the atopic status

	Nonatopic		Atopic	
	Controls	Patients	Controls	Patients
No. of subjects	20	9	29	19
Age (yr)				
Range	23-54	19-75	31-61	17-82
Mean	40.7	56.0	44.2	62.1
Sex M:F	2:18	4:5	9:20	12:7
Duration in Louisiana (yr)				
Range	0.6-54	0.1-30	0.2-53	1-79
Mean	32.6	13.7	24.3	30.9
Duration of leprosy (yr)				
Range		2-43		4-65
Mean		28.1		38.0
IgE range (IU/ml)	1.63-80.7	11.3-1821	5.2-2043	16.1-6389
IgE $\bar{G}\bar{X}$ (IU/ml)	18.9	72.9	96.3	296.1
$\bar{G}\bar{X} \pm SE$	14.8-24.2	44.2-120.1	72.0-128.8	193.8-452.4
<i>p</i> For IgE $\bar{G}\bar{X}$ (one-tail <i>t</i> test)		<0.01		<0.025
<i>z</i> Score	0.103	0.957	0.377	0.963
SE of <i>z</i> score	0.148	0.296	0.194	0.201
<i>p</i> Of <i>z</i> score (one-tail Student's <i>t</i> test)		<0.01		<0.05

elevated in all types of leprosy,^{1,5-7} in the lepromatous type only,² or in newly diagnosed patients.⁸ To the best of our knowledge, there are no studies of the atopic status of patients with leprosy or of the presence of IgE antibodies specific to *Mycobacterium leprae*. With RAST, Nuti et al.⁷ did not detect IgE antibodies against leprosin. Hamburger et al.⁸ believed that elevated levels of nonspecific IgE might block the passive transfer (Prausnitz-Küstner) reaction in patients with leprosy.

In our study we compared patients with leprosy with control subjects regarding the atopic status, serum total IgE, and the specificity of IgE to common allergens and to *M. leprae* antigen.

MATERIAL AND METHODS

All patients and staff at the Gillis W. Long National Hansen's Disease Center at Carville, La., were informed about the study, which was approved by the Institutional Review Boards of both the Louisiana State University School of Medicine in New Orleans and the National Hansen's Disease Center. All volunteers received full disclosure and signed informed consent forms, which were provided in both English and Spanish. Twenty-eight residential patients and 49 staff control subjects volunteered for the study. Demographic data are summarized in Table I.

For patients with leprosy, the type (lepromatous, tuberculoid, or borderline), activity (active or inactive), and duration of the disease were ascertained from the medical

records. Noted also were the results of stool analysis for ova and parasites, white blood cell count, and percent of circulating eosinophils. The average duration of leprosy in the patients was 34.8 years. Among the 28 patients, the disease was lepromatous in 26, tuberculoid in one, and borderline in one patient. In three lepromatous patients the disease was considered active, that is, intact organisms had been demonstrated in skin scrapings within the last year.⁹ Medications taken by more than one patient included dapsone (18), clofazimine (11), and acetylsalicylic acid (6); acetaminophen, oxycodone, and pseudoephedrine (four each); cimetidine, dexbrompheniramine, hydrochlorothiazide, and phenylpropanolamine (three each); alpramethyldopa, atenolol, brompheniramine, prednisone, propoxyphene, and thalidomide (two each). Medications taken by only one patient each were propranolol (Inderal; Ayerst Laboratories, New York, N.Y.), rifampin, pentoxifylline, triamterene, methylphenidate, clorazepate, flurazepam, sulindac, cephalexin, penicillin, captopril, furosemide (Lasix; Hoechst-Roussel Pharmaceuticals, Somerville, N.J.), clemastine, tetracycline, albuterol metered-dose inhaler, triprolidine, ibuprofen, codeine, conjugated estrogens, diphenhydramine, piroxicam, hydroxychloroquine, glyburide, amitriptyline, and temazepam.

Skin testing

Scratch testing was done on the flexor aspect of the patients' and control subjects' forearms with 20 common allergens (Hollister-Stier Laboratories, Spokane, Wash.), selected according to our experience in the allergy clinic.

Allergens included house dust, *Dermatophagoides farinae*, cat-hair dander, dog-hair dander, *Alternaria tenuis*, *Curvularia spicifera*, *Helminthosporium maydis*, giant ragweed, short ragweed, Mexican tea, redtop grass, Bermuda grass, Bahia grass, white ash, American elm, pecan pollen, black willow, cow's milk, egg white, and peanut. Subjects were prohibited use of antihistamines for 48 hours before the skin testing; none were using hydroxyzine or astemizole. The skin reactions were graded 0 to 4+ as compared with 50% glycerol diluent (negative control) and histamine 1 mg/ml (positive control).¹⁰

IgE measurement

Whole blood cell samples obtained from the patients were centrifuged on the day of collection, and the serum was kept frozen at -20° C. Phadebas IgE PRIST RIA (Pharmacia Diagnostics, Piscataway, N.J.) was used. All assays, undertaken simultaneously after completion of the clinical part of the study, were done in duplicate, and the average of the pair was used for statistical analysis. In none of the samples did the intrapair difference exceed 20% of the mean. Whenever the IgE level exceeded the linear portion of the standard curve, the sample was diluted tenfold and retested.

RAST for common allergens

All sera were tested for specific antibodies to 10 common allergens, namely, *D. farinae*, *A. tenuis*, giant ragweed, redtop grass, Bermuda grass, Bahia grass, white ash, cow's milk, egg white, and peanut. We used a paper disk RIA technique (Phadebas RAST, Pharmacia Diagnostics), and the results were scored 0 to 5+ according to the manufacturer's instructions.

M. leprae antigen preparation

Purified, irradiated, armadillo-derived *M. leprae* were obtained through the National Institute of Allergy and Infectious Diseases, National Institutes of Health, contract AI-52582. We suspended 20 mg of bacilli in 7 ml 0.01 mol/L of phosphate-buffered normal saline and disrupted by sonication, as described previously.^{11,12} After the sonicate was centrifuged at 10,000 g for 10 minutes, the pellet (designated ML10kP) was resuspended in 7 ml of phosphate-buffered saline. The supernatant from the 10,000 g centrifugation was centrifuged again at 100,000 g for 60 minutes. The resultant supernatant (designated ML100kS) was filtered through a 0.22 µm (pore size) membrane and stored at -20° C. Protein concentrations of ML10kP and ML100kS were determined according to the method of Lowry et al.¹³

Immunoblot for IgE antibody

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis and immunoblotting were done, as described previously.¹² Human IgE antibody was detected with peroxidase-labeled goat antihuman IgE, H-chain specific (ICN Biomedicals, Inc., Costa Mesa, Calif.). Immunoblots probed for antibodies of the other immunoglobulin subtypes were de-

veloped with peroxidase-labeled goat antihuman IgG, IgA, and IgM (Dako Corp., Santa Barbara, Calif.), as described previously.¹¹ Some patients' sera were absorbed with protein A to remove IgG antibody before probing for IgE antibody to *M. leprae*. Briefly, 100 µl of sera was incubated repeatedly with an equal volume of protein A-Sepharose CL-4B (Sigma Chemical Co., St. Louis, Mo.) containing protein A sufficient to bind 2 µg of human IgG until immunoblots became negative for IgG reactivity.

M. leprae RAST

M. leprae sonicate ML100kS, prepared as described above, was bound to filter paper disks activated by cyanogen bromide.¹⁴ The antigen-coated disks were used in the standard RAST assay, just as with the assay for IgE antibodies to the other allergens.

Statistical analysis

All IgE levels were converted to their natural logarithms for statistical analysis and calculation of each Gx. The F test of the variance ratio was used first to determine the type of Student's *t* test to be followed for testing the difference between two sample means.¹⁵ In no case was the result of the F test significant; therefore, Student's *t* test for independent samples with assumed equal variances was used. To ensure that the differences noted between these means were not due to age or sex differences between the groups, each log IgE was standardized (Z score) for age, sex, and atopic status with the normal values of a large population study¹⁶ and the following formula¹⁷:

$$Z = \frac{\text{Log serum IgE} - \text{Mean log serum IgE of matched group}}{\text{SD log serum IgE of matched group}}$$

The two-sample Student's *t* test for equal variances was used for all comparisons of the Z scores, whereas the one-sample test for the mean of a normal distribution with known variance was used to test the significance of the Z scores. Since previous studies suggested that patients with leprosy would not have IgE levels lower than levels of the control subjects, one-tailed testing was used for all *p* determinations except those for the significance of the Z scores of the control groups. A *p* value of <0.05 was considered significant.

RESULTS

Atopic status

Most of the patients and control subjects reported having histories suggestive of allergy symptoms. At the time of physical examination, however, many of the subjects did not have clear-cut signs of allergy. Some patients were noted to have atrophic, immobile skin and/or absence of the nasal turbinates and septum. We therefore arbitrarily based the atopic status on a positive result on the scratch test (2+ or greater) to at least one of the allergens used. Fourteen patients who had anesthesia of the forearms or hands had ab-

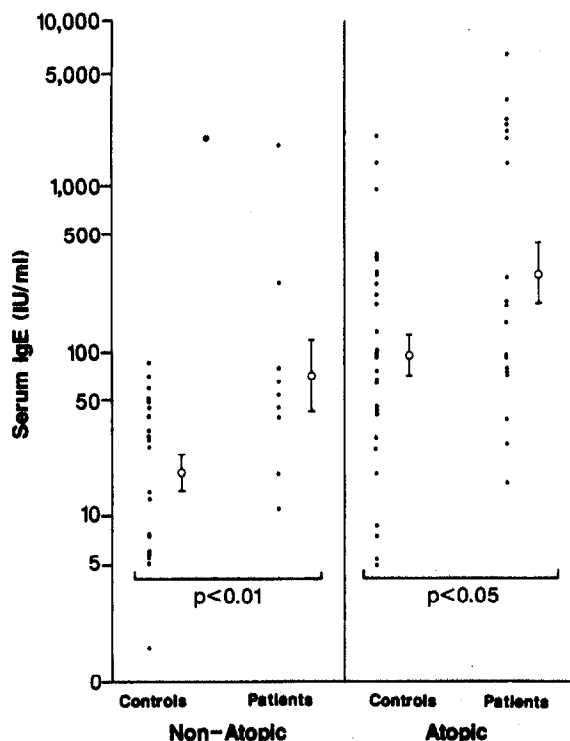


FIG. 1. Distribution and $\bar{Gx} \pm$ standard error of serum total IgE level in patients with leprosy and control subjects according to atopic status.

sent flare responses to allergen extracts as well as to histamine. Three such patients and one control subject who had negative skin responses were considered atopic because they had positive RAST responses (2+ or greater) to three or more allergens. One of these three patients had active lepromatous leprosy and was being treated with thalidomide to suppress an erythema nodosum leprosum reaction. This patient's eosinophil count (825 per cubic millimeter) and total IgE level (2279 IU/ml) were within the range of the whole leprosy group. He had received treatment for helminthiasis 4 months earlier, and his stool examination 1 month before the study was negative for parasites. Another patient receiving thalidomide, however, had positive skin tests to histamine and multiple allergens. The two patients with tuberculoid and borderline leprosy had eosinophil counts and IgE levels within the ranges of the 26 patients with lepromatous disease and therefore were included in the statistical analysis of the whole group.

In the patients with leprosy, the mean blood eosinophil count was 327.8 per cubic millimeter in the atopic group and 192.0 per cubic millimeter in the nonatopic. This difference, however, was not statistically significant ($p > 0.05$). No active or recent hel-

minthic infection was noted, except in the patient mentioned above.

Atopy was considered to be present in 19 of the 28 patients (68%) and in 29 of the 49 control subjects (59%), but the difference between the two groups was not statistically significant ($p > 0.05$). The three patients with active lepromatous disease had IgE levels of 206, 265, and 2279 IU/ml and eosinophil counts of 153, 0, and 825/mm³. They did not segregate into either the atopic or nonatopic groups. With the patients and control subjects considered separately, the differences in smoking status, sex, age, length of residence in Louisiana, and duration of leprosy between atopic and nonatopic groups were not significant, but the differences in age and sex ratios between patients and control subjects were significant ($p < 0.05$). To adjust for these demographic differences, we used the data of a large U.S. population study¹⁶ as a standard (Fig. 1).

Serum total IgE

The IgE $\bar{Gx}$ of all patients with leprosy was 188.7 IU/ml versus 49.6 IU/ml in the control subjects ($p < 0.001$). In both the atopic and nonatopic groups, the IgE $\bar{Gx}$ was significantly higher in the patients with leprosy than in the control subjects (Fig. 1). After standardization for age, sex, and atopic status, the differences between patients and control subjects persisted, $p < 0.01$ for the nonatopic group, $p < 0.05$ for the atopic group, and $p < 0.001$ for both groups combined (Table I).

The IgE $\bar{Gx}$ of both atopic and nonatopic patients was also found to be elevated significantly at 0.96 SD above the normal mean of the data of Barbee et al.,¹⁶ $p < 0.00001$ for both groups combined. The IgE $\bar{Gx}$ of the atopic control group was 0.377 SD above the mean, which was barely significant at $p = 0.04$. The IgE $\bar{Gx}$ of the nonatopic control subjects and that of all control subjects were not significantly higher than in the standard population.

M. leprae-specific IgE antibodies

No IgE binding to *M. leprae* sonicate was noted by either immunoblotting or RAST. Results of immunoblotting for IgE antibody to *M. leprae* were uniformly negative for all patients. By contrast, some patients tested positive for IgG or IgM antibody to *M. leprae* by immunoblotting. Serum from these patients was absorbed with protein A to remove IgG potentially capable of blocking antigenic sites for IgE antibody. In all cases, protein A absorption did not alter the negative binding results for IgE antibody to *M. leprae*. With RAST, some nonspecific binding of

radiolabeled anti-IgE to the disks occurred, but this was not abolished by heating at 57° C for 30 minutes and was not inhibited by adding the sonicate to the serum before incubation, indicating the absence of IgE antibodies specific to *M. leprae*.

DISCUSSION

According to the criteria used in the study, atopy was present in 68% of patients with leprosy and in 59% of control subjects, but the difference was not statistically significant. Both figures, however, are high, probably because of two main factors. First, the criterion used, that is, positive outcomes of skin testing or RAST to common allergens, rather than clinical symptomatology, and second, a selection bias of the subjects who volunteered for the study. Patients without atopic symptoms would be expected to be less likely to volunteer for testing.

Our observation of a significant rise of serum total IgE levels in patients with leprosy, regardless of the atopic status and in the absence of parasitic infestation, lends support to a similar finding reported by other investigators.^{1, 5-7} Probably this finding was not noted in other studies because of methodologic differences, such as the investigators' use of the IgE median instead of the $G\bar{x}$ level³ or the investigators not controlling for the presence of atopy and parasites.⁴ Our findings do not rule out the possibility that extremely high nonspecific IgE levels in newly diagnosed patients with active leprosy could block mast cell degranulation by common allergens.⁸ If such a phenomenon does occur, however, the effect may be lost later in chronic or inactive leprosy.

IgE production has been known to be enhanced by parasitic infestations, several types of viral illnesses, and certain fungal infections.^{18, 19} That a chronic bacterial disease such as leprosy is associated with increased IgE production is worthy of note. To the best of our knowledge, no other bacterial infection has been reported to increase IgE production; this phenomenon is worth exploring. It is possible that leprosy is peculiar because of the prominent skin involvement that in itself might cause a polyclonal IgE enhancement, as is the case with atopic dermatitis and some other skin diseases.^{18, 19} Another point for possible investigation would be whether IgE has a role, favorable or unfavorable, in the chronicity of leprosy.

At the plasma cell level, IgE synthesis is regulated by T cell-produced factors that either enhance or suppress IgE synthesis.²⁰ Patients with leprosy often have various degrees of T cell dysfunction²¹ that might be contributing to the increased IgE production. The disease, at least the lepromatous type, may also be as-

sociated with suppressed production of interferon- γ .²² The latter substance has been found to down regulate IgE synthesis as well.²³ Further studies, particularly on abnormalities in T cell subset functions or possible increase in interleukin-4 production, might clarify the underlying mechanism of increased IgE production in patients with leprosy.

None of the previous studies examined the serum of patients with leprosy for possible presence of IgE antibodies specific to *M. leprae* protein. In our study, we could not demonstrate such specificity, either by use of a solid-phase RIA (RAST) or an immunoblot technique. Although this finding suggests an enhanced nonspecific IgE production, we may not have used the appropriate antigen for detection of IgE antibodies. The antigen might be an altered *M. leprae* protein, a bacterial product, or a breakdown of tissue protein. Also, the lack of a positive control contributes to our uncertainty about the *M. leprae*-specific IgE antibodies, particularly by the RAST assay. Our immunoblotting technique, however, could detect antibodies of the IgM and IgG isotypes. Further studies are needed in this area as well.

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