

IgE in Leprosy; Effect of a *Mycobacterium leprae*-BCG Vaccine¹

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The measurement of levels of total serum IgE in leprosy patients is of considerable interest, due in part to the two following observations: Firstly, a state of generalized immunodepression, that appears to primarily affect T lymphocyte activity, has been reported in the lepromatous form (LL) of the disease (13, 22, 26). Secondly, elevated total serum IgE levels have been associated with immunodeficiency states that are either inborn or acquired, and this has been suggested to reflect a defect in T lymphocyte (particularly suppressor cell) activity (3, 12, 17, 28). These two situations may, therefore, explain the increased concentrations of IgE that have been reported in leprosy (21).

This possibility is, however, still open to question since a number of studies have demonstrated neither a generalized non-specific immunodeficiency in LL (7, 9, 13, 27) nor significantly elevated IgE levels when compared to the correct controls (2, 14, 25). Because intestinal helminthiasis can cause marked increases in total serum IgE levels, the non-lepromatous comparison group must be selected with great care (14). We undertook, therefore, a controlled study of serum IgE in LL, and also evaluated the effect of treatment with a *Mycobacterium leprae*-BCG vaccine.

MATERIALS AND METHODS

Study group. The patients were selected from a large group under treatment and evaluation by the Instituto Nacional de

Dermatología, Caracas, Venezuela. Groups of adults of balanced age, sex, and socio-economic level were examined, and the patient groupings were as follows: 47 with active lepromatous leprosy, as defined by clinical, histopathological, and immunological criteria (7, 9, 27). Sera were collected from these individuals both shortly before, and soon after, treatment with a series of injections of a live BCG plus killed-*M. leprae* vaccine (5, 6, 10, 11).

A group of 16 tuberculoid leprosy (TL) patients (TT + BT) were also studied, as were 32 household leprosy contacts, 16 of whom were positive in the Mitsuda test (8).

As comparative controls, 63 persons drawn from the same socio-economic level as the leprosy patients but with no known contact with the disease were examined.

Total serum IgE assay. The technique of Ceska, *et al.* (4) was used, and while being developed in our laboratory, was standardized against the commercially available "Phadebas" (Pharmacia, Sweden) test. Briefly, rabbit anti-IgE was coupled to CNBr-activated paper discs, which were then incubated with the test sera for 6 hr. After washing, the discs were exposed to ¹²⁵I-labelled anti-IgE for 18 hr. After further washing, the discs were counted in a gamma counter and the cpm compared to those from discs prepared by incubation with standard concentrations of IgE, in place of test sera.

Statistical methods. Determination of coefficients of the 3rd and 4th moments about the mean (skewness and Kurtosis) demonstrate that IgE concentrations do not form a normal distribution. They were, therefore, normalized by logarithmic (base 10) transformation, and then the means and standard deviations calculated, these being compared between groups by the Student's *t* test. Lack of statistical significance under these conditions was also confirmed by non-parametric analysis (Wilcoxon-Mann and Whitney tests) of the raw data.

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TABLE 1. Total serum IgE levels in various study groups.

Group	No.	Mean \pm S.D. ^a	Geometric mean IU/ml
Contacts			
Mitsuda negative	16	2.04 \pm 0.37	110
Mitsuda positive	16	2.33 \pm 0.53	214
Whole group	32	2.19 \pm 0.54	155
Tuberculoid leprosy	16	2.52 \pm 0.43	331
Lepromatous leprosy			
Before vaccination	47	2.66 \pm 0.61	457
After vaccination	47	2.62 \pm 0.65	417
Normal controls	63	2.43 \pm 0.59	267

^a Log (IU/ml).

For descriptive purposes, the antilogarithm of the mean log IgE (geometric mean) concentration is presented. Changes in IgE levels in individual LL patients were expressed as ratios (level after vaccination/level before), and the reciprocal presented when < 1 .

RESULTS

The levels of total serum IgE in the various groups studied are presented in Table 1. Although a tendency toward higher levels was noted in the patients suffering from active lepromatous leprosy, no statistically significant differences were detected between these patients and those with tuberculoid leprosy, or individuals who were household contacts, whether Mitsuda reaction positive or negative. Although the IgE levels were generally high in these groups, they were no more so than in persons of a comparable socio-economic level but with no known contact with leprosy.

In Table 2 can be seen the changes in total serum IgE levels in LL patients during the course of vaccination with *M. leprae*-BCG. No change occurred in 15.0% of the patients, while equal proportions (42.5%) showed either an increase or a decrease.

The results presented in Table 3 demonstrate that there was no relation between either the number or time period of vaccinations and alterations in IgE concentrations. The changes noted were, in fact, closely comparable to those seen in apparently normal individuals over an equivalent time period (results not presented).

TABLE 2. Changes in total serum IgE levels in vaccinated lepromatous leprosy patients.

No.	Change ^a			
	Direction	Max.	Min.	Mean \pm S.D.
20	Increase	10.00	1.11	2.31 \pm 2.25
7	None	0	0	0
20	Decrease	12.50	1.12	1.96 \pm 3.85

^a Change expressed as ____ fold increase or decrease after *M. leprae*-BCG vaccination.

DISCUSSION

In some previous studies, high levels of total serum IgE have been detected in leprosy patients (^{18, 20, 21, 24}). A possible explanation for this (²¹) is provided by the reported generalized suppression of T lymphocyte function in LL (^{13, 22, 26}), and the association of elevated IgE concentrations with immunodeficiency, particularly at the T cell level (^{3, 12, 17, 28}). That the situation is not straightforward was suggested, however, by reports that the immune defect in LL patients is restricted to *M. leprae* (^{7, 9, 13, 27}) and that concurrent intestinal helminthiasis might be the cause of the elevated IgE levels in these patients (^{14, 15, 25}). Although in some studies the possible influence of nematode infections was considered, the augmented IgE concentrations were still attributed to an effect of the lepromatous disease (^{18, 20, 21}). However, in some studies the comparison groups have been composed of individuals of a higher socio-economic status than the patients. Even if the lepromatous group were not suffering intestinal helminthiasis at the time of examination, previous infections might have contributed substantially to the actual IgE

TABLE 3. Number and period of vaccinations of lepromatous leprosy patients, related to changes in total serum IgE levels.

Change	Vaccinations ^a	
	No.	Period
Increase	4.6 \pm 1.5	14.0 \pm 3.6
None	5.3 \pm 0.5	16.4 \pm 2.6
Decrease	4.3 \pm 1.5	14.5 \pm 4.5

^a Mean \pm S.D. Period = months between first and latest vaccination with *M. leprae*-BCG.

levels in these patients. In the group of individuals with active lepromatous leprosy that we examined, the concentrations of total serum IgE were relatively high, but although the geometric mean value was 2.5 times greater than that of the control groups, this was not statistically significant. Our controls were a) household leprosy contacts who were either Mitsuda test positive or negative, and b) individuals of a comparable socio-economic level but with no known contact with the disease. It should be remarked here that the importance of the appropriate statistical tests in the analysis of data with a non-normal distribution (as for IgE levels) has rarely been considered in previous studies.

If elevated IgE production is related to a generalized state of T cell anergy (3, 12, 17, 28), and this condition occurs in LL (13, 22, 26), then the levels of this immunoglobulin should be greater in these patients than in tuberculoid leprosy (TL) patients, in whom T cell responsiveness is generally considered to be intact (7, 9, 13, 22, 26, 27). Previous reports have mentioned slightly higher IgE concentrations in LL than TL (14, 20, 25) but, as in our study, this was not significant. In other studies, no differences between the two disease forms were shown (21, 24).

As a final demonstration of the lack of relation between elevated IgE and the immunologic defect in LL, we examined patients after they had received a series of injections of a *M. leprae*-BCG vaccine. While this treatment can provoke clear clinical, histopathological, and immunological changes (5, 6, 10, 11), no effect upon total serum IgE levels was noted. In other diseases where high IgE production has been related to a deficiency in T cell activity, restorative procedures, such as treatment with transfer factor, have been found to cause decreases in the level of this immunoglobulin (16, 29). A comparable effect has also been mentioned in leprosy (23), and the report that leprosy patients appear to have defective suppressor T cell activity (1) raises the question as to why no change was observed in our study. This is probably due to the fact that Venezuelan (and various other) LL patients do not show evidence of a generalized non-specific T cell anergy (7, 9, 13, 27). In addition, comparison of the total IgE levels reported here with those of Africa or Asia

(14, 21, 25) reveal that the Venezuelan values are relatively low. These differences might be due to the operation of racial or social factors (15, 19), which could also explain, at least in part, the lack of agreement between some of the published studies.

SUMMARY

Since some previous studies have reported elevated total serum IgE levels in leprosy, that may be associated with the existence of a state of generalized T cell anergy, we undertook a carefully controlled study of this immunoglobulin in such patients before and after treatment with a *Mycobacterium leprae*-BCG vaccine.

We found, firstly, that lepromatous leprosy patients suffering active disease had only a moderate elevation of IgE levels that was not statistically significant when compared to appropriate controls. In addition, multiple injections of the vaccine did not cause alterations in the concentration of this immunoglobulin. We were, therefore, unable to confirm the possible existence of a generalized immunodeficiency in lepromatous leprosy that could cause hyper-production of IgE.

RESUMEN

Puesto que algunos estudios previos han indicado una elevación en los niveles séricos de IgE en lepra que puede estar asociada a la existencia de una anergia generalizada de células T, decidimos efectuar un estudio cuidadosamente controlado de esta inmunoglobulina en tales pacientes antes y después de su tratamiento con una vacuna preparada con *Mycobacterium leprae* y BCG.

Encontramos que los pacientes con lepra lepromatosa que sufren de la enfermedad activa mostraron sólo una moderada elevación en sus niveles de IgE que no fue estadísticamente significativa cuando se comparó con los controles apropiados. Las inyecciones múltiples de la vacuna tampoco causaron alteraciones en las concentraciones de esta inmunoglobulina. Por lo tanto, en este estudio fuimos incapaces de confirmar la posible existencia de una inmunodeficiencia generalizada en lepra lepromatosa que pudiera causar hiper-producción de IgE.

RÉSUMÉ

Les études précédentes ont révélé une augmentation des taux d'IgE du serum dans la lèpre, qui pourrait être associée avec la présence d'un état d'anergie généralisée des cellules T. On a dès lors entrepris une étude soigneusement contrôlée de cette immunoglobuline chez

des malades avant et après traitement par un vaccin combinant *Mycobacterium leprae* et le BCG.

On a tout d'abord observé que des malades souffrant d'une lèpre lépromateuse active ne présentaient qu'une élévation modérée des taux de IgE et qui n'était statistiquement significative lorsqu'on la comparait à des témoins appropriés. De plus, des injections multiples du vaccin n'ont pas entraîné d'altérations dans la concentration de cette immunoglobuline. Par conséquent, il n'a pas été possible de confirmer l'existence éventuelle d'une immuno-déficience généralisée dans la lèpre lépromateuse, qui pourrait entraîner une surproduction d'IgE.

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