Immunologic Aspects of Leprosy With Special Reference to the Study of Immunoglobulin E[1]

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The association of high level of serum IgE with allergic ([10]) and parasitic diseases ([5]) has been known since its identification as a carrier of reaginic activity. The concentrations of several classes of immunoglobulins, almost invariably IgA, sometimes IgG, and IgM, are elevated in the sera of the patients with lepromatous leprosy ([24]). These patients often suffer from profound depression of cell-mediated immunity ([23]).

It is generally agreed that certain populations of B cells need the cooperation of T cells to synthesize IgG ([4]). Such cooperation is also required for the production of IgE which carries reaginic activity ([18]). Moreover, the patients suffering from lepromatous leprosy have T cell deficiency ([6]). In view of these concepts, the concentrations of serum IgE in leprosy patients have been compared with those obtained in the normal population and patients with helminthiasis.

MATERIALS AND METHODS

Selection of controls. Two types of controls have been included in the present study.

Normals. Thirty-five apparently healthy adults, ages ranging from 18 to 35 years, who neither showed parasites in their stool nor presented family and personal histories of allergy, were selected from high socioeconomic strata; e.g., medical students, physicians and their wives. Their sera were exclusively used as controls for serum IgE. Another 70 normal healthy subjects were also included for determining normal serum levels of immunoglobulins IgG, IgA, IgM and IgD.

Helminthiasis. Thirteen patients with microfilaria in their peripheral blood without any evidence of elephantiasis, along with 12 patients giving histories of passing adult roundworms in their vomitus and/or stool, and ova in their feces, were selected as another group of controls.

Selection of patients with leprosy. Seventy-eight patients with lepromatous and tuberculoid leprosy were selected on the basis of clinical history, physical examination and skin biopsy ([17]) from the Indian Army Leprosy Home, Agra; the Japanese Leprosy Mission, Agra; and the Leprosy Home, Shahdara, Delhi. Patients with borderline lesions, as defined by the Ridley-Jopling classification, were grouped together with tuberculoid or lepromatous form of illness. There were 78 leprosy patients including 41 tuberculoid (TT, 29 cases; BT, 12 cases), and 37 lepromatous cases (LL, 23 cases; BL, 14 cases). Borderline and indeterminant cases were not included in the present study. Among them, 54 denied personal and family history of allergy and did not exhibit immediate skin reaction to intradermal tests with a battery of 70 common allergens. Among these 54 patients, IgE was determined only in the sera of the 24 lepromatous and 13 tuberculoid leprosy patients for whom repeated stool examination was possible. IgG, IgA, IgM and IgD were estimated in the sera from all the above 78 leprosy patients.

Determination of immunoglobulins. The four classes of serum immunoglobulin, IgG, IgA, IgM and IgD were studied by the method of single radial diffusion in agar gel ([15]). Anti-IgG, anti-IgA, anti-IgM and anti-IgD antisera along with their reference standards were procured commercially from the Meloy Laboratories, U.S.A. To determine the levels of serum IgE, dual technics employing both direct and indirect methods using a commercially available human IgE kit (Meloy Laboratories, U.S.A.) and radioactive single radial immunodiffusion ([19]) were used. Details of the methods have been described elsewhere ([22]). Serum immunoglob-

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TABLE 1. *Comparative study of serum IgE in leprosy and parasitic disorders.*

Groups	No. of subjects	Serum IgE[a]	No. having IgE < 700 I.U.	t value
1. Normals	35	1025 ± 2103 (< 40 - 8500)	26	
2. Leprosy				
a) tuberculoid	13	5150 ± 3850 (< 40 - 16000)	1	*vs* 1 = 3.3
b) lepromatous	24	5197 ± 1871 (72 - 9000)	3	*vs* 2a = 0.04 *vs* 1 = 7.9
3. Helminthiasis				
a) ascariasis	12	7328 ± 3400 (< 40 - 12000)	4	*vs* 1 = 13.7
b) filariasis	13	4244 ± 2600 (350 - 10000)	4	*vs* 1 = 4.0 *vs* 3a = 2.5

[a] I.U. per ml, mean ± SD and range.

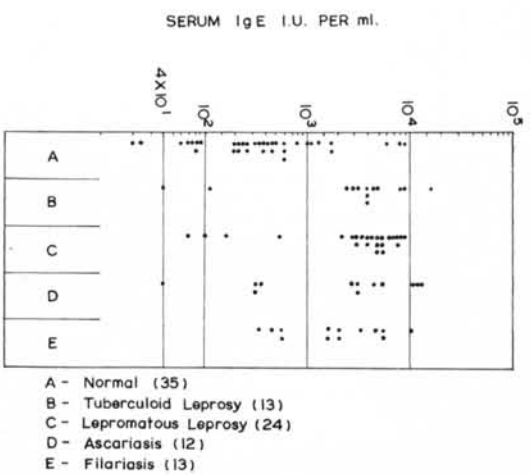

FIG. 1. Serum IgE levels in normal Indian subjects and in patients with leprosy and parasitic infestation.

ulin levels of these leprosy patients were compared with those found in the normal subjects as well as in the patients with helminth infestations. The data thus obtained were statistically evaluated.

RESULTS

Serum IgE levels were estimated in only those individuals with leprosy whose repeated stool examinations made possible the exclusion of parasitic infestation since hookworm infection is commonly encountered in these leprosy homes. The results of serum IgE levels in the normal Indian subjects and patients with leprosy are shown in Table 1 and Figure 1.

The mean serum IgE levels were raised in both types of leprosy, lepromatous as well as tuberculoid forms, by more than five times that found in the normal subjects (Table 1). Only 25.8% of the normal subjects had serum IgE levels above 700 I.U. per ml. In contrast, 62.5% of the lepromatous and 38% of the tuberculoid leprosy patients possessed circulating immunoglobulin IgE levels of more than 4,000 I.U. per ml. The highest value of serum IgE level (16,000 I.U. per ml) was observed in a patient with tuberculoid leprosy (Fig. 1). Two patients with tuberculoid leprosy and four patients with lepromatous leprosy had normal levels of serum IgE (Fig. 1). No significant difference was found between the mean serum IgE levels of these two types of the disease.

Among other classes of serum immunoglobulins, there was a marginal rise of IgM in only the lepromatous form while circulating IgG and IgA were significantly elevated in both forms of the illness (Table 2). Serum IgD was detected in 24% of tuberculoid and 32.5% of lepromatous leprosy patients, and in 50% of the normal subjects.

The mean serum IgE level (7,328 I.U. per ml) in the patients with roundworm infestation was elevated seven times that observed in the normal controls, while that observed in the patients with filariasis (4,244 I.U. per ml) was about four times higher than the average normal level (Table 1). Furthermore,

TABLE 2. *Serum immunoglobulins IgG, IgA, IgM and IgD in leprosy and helminthiasis.*

Groups	No. of subjects	Classes of immunoglobulins mg per 100 ml serum; mean ± S.D. (range)				% having IgD
		IgG	IgA	IgM	IgD[a]	
1. Normals	70	1076 ± 262 (250 - 1828)	122 ± 31 (37 - 348)	103 ± 22 (42 - 204)	16.5 ± 6.7 (1 - 33.4)	50
2. Leprosy						
a) tuberculoid	41	1198 ± 300 (820 - 1600) t *vs* 1 = 2.1	229 ± 107 (30 - 470) t *vs* 1 = 6.2	99 ± 13 (69 - 225) t *vs* 1 = 0.9	9.3 ± 9.6 (1 - 31.6)	24
b) lepromatous	37	1352 ± 290 (700 - 2000) t *vs* 1 = 4.8 t *vs* 2a = 2.3	255 ± 114 (80 - 470) t *vs* 1 = 6.9 t *vs* 2a = 1.04	135 ± 35 (68 - 207) t *vs* 1 = 5.7 t *vs* 2a = 6.0	10.6 ± 9.1 (1 - 27.5)	32.5
3. Helminthiasis						
a) ascariasis	12	1067 ± 144 (800 - 1360) t *vs* 1 = 0.23	108 ± 39 (40 - 168) t *vs* 1 = 1.4	187 ± 70 (77 - 315) t *vs* 1 = 5.0	22 ± 21 (1 - 53.4)	72.3
b) filariasis	13	1285 ± 117 (1000 - 1500) t *vs* 1 = 4.6 t *vs* 3a = 4.6	106 ± 36 (64 - 204) t *vs* 1 = 1.5	165 ± 44 (111 - 237) t *vs* 1 = 5.0 t *vs* 3a = 1.07	6.7 ± 4.8 (1 - 15.8)	77

[a] Serum IgD levels above 1 mg per 100 ml are described as detectable.

66.6% of the subjects with ascariasis and only 38.4% of the patients with filariasis had serum IgE concentrations above 2,500 I.U. per ml. The highest observed level of circulating IgE in ascariasis was 12,000 and that in filariasis was 10,000 I.U. per ml. Interestingly, 4 of the 12 patients with ascariasis and 4 of the 13 proved cases of filariasis had serum IgE levels below 700 I.U. per ml. Among other classes of serum immunoglobulins, IgM was raised in both ascariasis and filariasis, but significant elevation of serum IgG was observed only in filariasis (Table 2). IgD was detected in the sera of 72.3% subjects with ascariasis and in 77% of the patients with filariasis. In contrast, it was detected in only 50% of the normal subjects.

DISCUSSION

An elevated level of serum IgE in about 25% of apparently healthy Indian individuals with no family and personal history of allergy may be attributed to undetectable subclinical or past parasitic infections ([5]). Extremely high levels of serum IgE were reported in rural African populations and the mean level of serum IgE in the Ethiopian children was 20 times higher than that of the Swedish control group ([12]). A reported elevated serum IgE in 7% of normal European populations ([12]) may, however, be attributed to the fact that the production of IgE is not limited to parasitic and allergic disorders.

Regarding the second type of controls, the rise of serum IgE in the subjects with helminthiasis, though spectacular, is not universal. In the present study, although in ascariasis the mean serum IgE level was 7,328 I.U. per ml, in 4 of 12 such patients the serum IgE levels were below 700 I.U. per ml. Similarly, serum IgE levels were not found to be raised in all the 13 proved cases of filariasis. Four sera from each of these two groups of parasitic diseases which have IgE levels within normal limits, may belong to a group of IgE nonresponders in a situation similar to that in which about 20% of sera obtained from persons with schistosomiasis and larva migrans failed to give positive P-K reaction ([7]). Of the other classes of immunoglobulins, the mean levels of serum IgM were significantly elevated in both filariasis and ascariasis while IgG was only raised in filariasis. Also IgD was detected in more subjects with helminthiasis than in

normal persons. This differential pattern of the synthesis of the various classes of immunoglobulins by the hosts may indicate that the habitat of the worms, their life cycles and their antigenicity may influence the formation of these different classes of immunoproteins.

Common bacterial and viral infections do not seem to influence the serum IgE concentrations ([7]) but it has been claimed that bacterial polysaccharides and mycobacterial antigens introduced either by natural infection or by artificial immunization may induce the synthesis of reaginic type of antibodies ([7]). The present study shows that the mean serum IgE levels are significantly higher in patients with leprosy. It has not yet been possible to demonstrate high IgE levels in patients with other mycobacterial infections, such as fibrocaseous type of pulmonary tuberculosis ([21]), but it remains to be seen whether the elevation of serum IgE levels in leprosy patients is due to the stimulation by *M. leprae* antigens. Our findings suggest that the elevation of serum IgE in the patients with leprosy may not even be attributed to the possible parasitic infections as reported by Grabosz *et al* ([8]), although this possibility cannot be ruled out entirely despite our effort to eliminate parasites by careful stool examinations in all those cases.

Although the serum IgE is found to be increased in patients with minimal change nephrotic syndrome ([9]) and primary immunodeficiency states, such as the Wiskott Aldrich syndrome ([3]), and decreased in ataxia telengectasia and hypogammaglobulinemia ([2]), the way it contributes to the underlying mechanism of the disease process is still obscure.

An immunologic paresis, so often found in lepromatous leprosy ([27]), may have a role in this observed augmented IgE production. This notion contradicts the experimental finding in which T cells have been shown to be required by B cells in the production of reaginic type of antibody ([18]). It seems probable that a subpopulation of T lymphocytes has an important suppressor effect on B lymphocytes ([1]); although, there are T cells in lepromatous leprosy but their number is reduced ([6]). Thus, it is possible that the number of suppressor or controlling T cells might also be reduced, which leads to the emergence of hyperactive B cells. Parallel observation of elevated serum IgE levels in patients with Hodgkin's disease with severe impairment of cellular immunity was made recently by Rubenstein *et al* ([20]). Although there is no apparent significant difference between the mean serum IgE levels in lepromatous and tuberculoid leprosy patients, a closer look shows that a serum IgE concentration of more than 4,000 I.U. per ml is found in 62% of the former cases and in 38% of patients in the latter group. The high serum immunoglobulin IgE demonstrated in certain immunodeficiency states, such as the Wiscott-Aldrich syndrome ([3]), eczema ([16]), and malnutrition ([14]), in which cell-mediated immunity is found to be affected, may have a common underlying mechanism for the elevation of serum IgE. However, recent studies on regulatory mechanism in reagin synthesis suggest that thymocytes may either stimulate or suppress reaginic type of antibody formation in some nonspecific manner ([26]). This view is also supported by a recent study by Saha *et al* ([25]) who observed lowering of elevated serum IgE levels in lepromatous leprosy patients after immunologic reconstitution therapy by viable peripheral blood lymphocytes from normal blood donors. Further, a suggestion has been put forward recently that nonfunctional IgE antibody molecules may be found in the serum of some individuals ([13]), and helminth infections may also potentiate the production of these unrelated IgE antibodies in the seum ([11]), but the manner by which this occurs is not yet clear.

SUMMARY

The serum levels of IgG, IgM, IgD and IgE have been determined in normal subjects, individuals suffering from ascariasis and filariasis, and in leprosy patients. Allergic and parasitic diseases were excluded in these normal subjects and in leprosy patients before they were taken for the study of their serum levels of IgE. The circulating IgG was significantly raised in both tuberculoid and lepromatous forms of leprosy and also in filariasis; IgM was significantly elevated in only the lepromatous form of leprosy, ascariasis as well as in filariasis; while IgA was exclusively raised in both forms of leprosy. IgD was detected in the sera of more subjects with ascariasis and filariasis than in normal individuals and leprosy pa-

tients. The mean level of serum IgE in 35 normal Indian subjects was 1,025 I.U. per ml, 9 of them (25%) having serum IgE concentrations above 700 I.U. per ml. The highest mean level of serum IgE was found in ascariasis (7,328 I.U. per ml), followed by leprosy (5,180 I.U. per ml), and filariasis (4,244 I.U. per ml). Furthermore, no significant difference between the mean serum IgE levels of tuberculoid and lepromatous leprosy patients was observed. Although the rise of serum IgE level in these parasitic diseases, as well as in leprosy, was spectacular, the augmented synthesis of this unique class of immunoglobulins was not invariably present in all patients. The results have been discussed on the basis of recent ideas on immunoglobulin synthesis.

RESUMEN

Se determinaron los niveles sanguíneos de IgG, IgA, IgM, IgD e IgE en sujetos normales, individuos que sufrían ascariasis y filariasis y en pacientes con lepra. En los sujetos normales y en los pacientes con lepra se habían excluído enfermedades alérgicas y parasitarias, antes de estudiar sus niveles séricos de IgE. La IgG circulante estaba significativamente aumentada, tanto en las formas tuberculoides, como en las formas lepromatosas de lepra y también en la filariasis; la IgM estaba significativamente elevada sólo en la forma lepromatosa de lepra, en la ascariasis y en la filariasis; mientras que la IgA estaba elevada solamente en ambas formas de lepra. La IgD se detectó en el suero de más sujetos con ascariasis y filariasis que en individuos normales y pacientes con lepra. El nivel promedio de IgE sérica en 35 individuos normales, Indios, es de 1025 IU por ml, 9 de ellos (25%) tenían concentraciones séricas de IgE sobre 700 IU por ml. El nivel promedio más alto de IgE sérica, se encontró en individuos con ascariasis (7328 IU por ml), seguido por lepra (5180 IU por ml) y filariasis (4244 IU por ml). Aún más, no se observaron diferencias significativas entre los niveles séricos promedio de IgE entre los pacientes tuberculoides y lepromatosos. Aunque la elevación del nivel sérico de IgE en estas enfermedades parasitarias, como en la lepra, es espectacular, la síntesis aumentada de esta clase especial de inmunoglobulinas no se presenta en forma invariable en todos los pacientes. Los resultados se discuten en base a ideas recientes sobre la síntesis de inmunoglobulinas.

RESUME

Chez des sujets normaux, souffrant d'ascaridiase et de filariose et chez des malades de la lèpre, on a déterminé les taux sériques des IgG, IgA, IgM, IgD et IgE. Les affections allergiques et parasitaires ont été exclues chez ces sujets normaux, de même que chez les malades de la lèpre, pour l'étude des taux de IgE dans le sérum. Le taux des IgG circulant est significativement plus élevé tant chez les malades tuberculoïdes que chez les lépromateux, de même que dans la filariose. Les IgM sont significativement plus élevés dans la forme lépromateuse seulement, dans l'ascaridiase, et dans la filariose, alors que les IgA ne présentent une élévation du taux que dans la lèpre, et ceci, dans les deux formes de la maladie. On a plus souvent détecté des IgD dans le sérum d'individus souffrant d'ascaridiase et de filariose, que chez les individus normaux ou chez les lépreux. Le taux moyen des IgE du sérum chez 35 indiens normaux a été de 1025 UI par ml, 9 d'entre eux (25%) présentant une concentration sérique en IgE dépassant 700 UI par ml. Le taux moyen le plus élevé des IgE sérique a été observé dans l'ascaridiase (7328 UI par ml), et ensuite dans la lèpre (5180 UI par ml), et dans la filariose (4244 UI par ml). En outre, aucune différence significative n'a été observée entre les taux sériques moyens d'IgE chez les malades lépromateux et chez les malades tuberculoïdes. Quoique l'on puisse considérer comme spectaculaire l'élévation des taux sériques d'IgE dans ces maladies parasitaires, de meme que dans la lèpre, une augmentation de la synthèse de ce groupe unique d'immunoglobulines n'est pas toujours présente chex tous les malades. Les résultats ont été discutés sur la base des idées récentes concernant la synthèse des immunoglobulines.

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