Immunologic Aspects of Lepromatous Leprosy with Special Reference to the Study of Antibodies[1]

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The role of immunity in leprosy has attracted great interest. Studies of immune mechanisms in patients with lepromatous leprosy have indicated that these patients suffer not only from hyporeactive state of cell-mediated immune responses ([20]), but also from hyperreactivity of antibody-mediated immune mechanisms ([6]). The latter findings are based on tests which include complement fixation, hemagglutination, electrophoresis, precipitation and immunofluorescence, together with a variety of antigens not from lepromas, but also from *Mycobacterium tuberculosis* and other Actinomycetales. In view of these observations, a study of antibodies along with immunoglobulins and the rheumatoid factor has been undertaken in patients with lepromatous leprosy and the immunogenesis of the findings are discussed.

MATERIALS AND METHODS

The study group consisted of 40 patients with lepromatous leprosy, hospitalized in a leprosy home, Shahdara. The diagnosis was based on characteristic clinical and histopathologic features of their lesions. In all cases the ABO blood group, saline ABO isoagglutinin titer, and titers of antistreptolysin O (ASO), and the rheumatoid factor (RA factor), were studied while in 36 of the 40 patients immunoglobulins were also estimated. The control group consisted of 35 volunteers wthout signs of leprosy who were matched by age and sex. In all these persons immunoglobulins and the isoagglutinin titer were determined, and in 28 cases antistreptolysin O antibody was also estimated. In another 60 normal blood donor volunteers and in 30 patients with rheumatoid arthiritis, the rheumatoid factor was also studied.

ABO blood groups were detected by high titer anti-A, anti-B, and anti-AB (O group) sera. Saline ABO isoagglutinin titer was estimated utilizing the tube dilution method of Mollison ([15]). In cases with missing isoagglutinins, the tests were repeated thrice and then the possibility of weak A and B isoantigens was ruled out by anti-A_1 lectin (*Dolichus biflorus*), and anti-H lectin (*Ulex europaeus*), after the technic described in *Hyland Reference Manual of Immunohematology* ([10]).

Serum levels of IgG, IgM, IgA, and IgD immunoglobulins were determined by the method of single radial diffusion in agar gel ([14]) and the data were statistically evaluated. Titers of ASO and the rheumatoid factor were estimated after the methods of Baker ([1]) and the latex fixation kit of Sylvania.

RESULTS

ABO blood groups and isoagglutinin titer were estimated in 35 normal individuals and 40 leprosy patients. The isoantibody level varied between 1/16 to 1/64 dilution in normal persons and between 1/2 to 1/32 in 29 leprosy cases. Of the remaining 11 leprosy patients, in whom isoagglutinins could not be detected, there were five, three, and three individuals with A, B, and O blood groups respectively (Table 1). The isoagglutinin titer endpoint was 1/16, 1/32, and 1/64 dilution in 13, 13, and 9 controls in order of frequency. Of the 29 leprosy patients with demonstrable isoantibodies in the serum, the titer dilution endpoint was 1/2 in two, 1/4 in ten, 1/8 in six, 1/16 in seven, and 1/32 in four cases.

Quantitative analysis of immunoglobulins was done on 36 leprosy patients and 35

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TABLE 1. *ABO isoagglutinin levels in controls and leprosy patients.*

Group	No. of cases studied	Level of isoagglutinin by dilution in number of cases						
		0	1/2	1/4	1/8	1/16	1/32	1/64
Control	35	—	—	—	—	13	13	9
Leprosy	40[a]	11	2	10	6	7	4	—

[a] There were 11, 10, 17, and 2 cases of A, B, O, and AB blood groups respectively. The isoantibodies were missing in 5, 3, and 3 patients of A, B, and O groups in order of frequency.

normal individuals. The levels of various immunoglobulins are shown in Table 2. It is evident that IgM and IgA globulin levels were significantly higher in leprosy patients while IgD and IgG levels were higher in normal individuals, although the differences are not statistically significant.

Antistreptolysin O titer and the rheumatoid factor were estimated in all the leprosy patients. The rheumatoid factor was positive at 1/20 dilution in 35%, 3.3%, and 43% of leprosy cases, normal individuals and rheumatoid arthritis patients respectively. ASO titers were within the range of 50 to 250 Todd units in 37% of the patients and varied between 333 to 1,250 Todd units in the remaining 63% of the cases. The range of ASO titers, estimated in 28 healthy adult individuals, had been between 12 to 333 Todd units.

DISCUSSION

Buck and Hasenclever (4) studied anti-ABO isoagglutinin titers in patients with leprosy and reported higher titers in lepromatous leprosy cases with A or B blood groups than the patients with tuberculoid leprosy or controls. No difference in the isoagglutinin titers was observed between leprosy cases and controls with blood group O. On the contrary, in the present series the patients of lepromatous leprosy were found to have low isoagglutinin titer in general and missing isoantibodies in 28% of the cases. Also, no difference in the isoantibody titers of the patients with various blood groups has been observed. The reasons for the discrepancy between the two studies are not evident. In adult human beings anti-A and anti-B isoantibodies are almost invariably present in blood when corresponding isoagglutinogen is absent. Missing isoagglutinins are very rare and occur only about once in 10,000 cases (8). The absence of isoagglutinins usually has some interesting explanations: they may, i.e., be the first indication of the phenotype Am, of a chimera, of dispermy, or of hypogammaglobulinemia (17). Isoagglutinins may be weak or absent in chronic lymphocytic leukemia, myelomatosis (12, 19, 23), and the Wiskott-Aldrich syndrome (9).

Quantitative analyses of immunoglobulins have shown raised levels of immunoglobulin IgA and IgM in lepromatous leprosy patients as compared to controls. Similarly, a marginal increase in the level of IgM in patients with lepromatous leprosy has been reported (3, 13). A study of the rheumatoid factor indicated strongly positive tests in 35% of the patients. It is well-known that both the rheumatoid factor and natural saline ABO isoagglutinin are functions of immunoglobulin IgM. Thus, it is suggested that immunoglobulin IgM has shown functional dichotomy in these patients. An antibody response to natural streptococcal infection in leprosy patients is also evident by raised ASO titer as is observed in normal subjects. These observations further suggest that there is deficient response to natural blood group isoantigen but not to streptococcal antigen or autoantigen. Analysis of these findings suggests that the disease process in lepromatous leprosy has probably suppressed the function of the clones with previous immunologic experience, committed for isoantibody production due to the preoccupation of the immunological system with other functions during stress. A similar speculation analyzing the immunogenesis of Kveim reaction in sarcoidosis has been made by Lawrence and Valentine (11).

It is established that lepromatous leprosy is associated with generalized depression of

TABLE 2. *Immunoglobulin levels in controls and lepromatous leprosy patients*

Values	Immunoglobulins in mg%							
	IgG		IgM		IgA		IgD	
	Control	Leprosy	Control	Leprosy	Control	Leprosy	Control	Leprosy
Mean	976.2	935.9	104.1	128.1	208.3	309.9	14.1[a]	9.4[b]
Variation	(410-1540)	(240-1540)	(57-160)	(72-170)	(57-299)	(201-462)	(0.0-45.4)	(0.0-38.7)
Standard deviation	±287.8	±293.2	± 33.28	±32.1	±63.7	± 51.3	±17.5	±11.4
"t"	0.57	0.3055	3.0	2.66	7.55	7.3	1.34	0.8
"p"		>.05		<.01		<.01		>.05

[a,b] Quantitative analysis of immunoglobulins was done in 36 lepromatous[b] leprosy patients and 35 normal[a] subjects. IgD was not detectable in 20 controls and in 15 leprosy patients. It was present in traces in one control and three leprosy patients.

cell-mediated immunity as indicated by various skin tests ([4, 5]), lymphocytic response to PHA, SLO and various mycobacterial antigens ([7, 16,18]), and depletion of lymphocytes in thymus-dependent paracortical regions ([21]). It has also been reported that a variable number of lepromatous leprosy patients respond to some antigens but fail to exhibit delayed sensitivity to other antigens at the same time ([5, 22]). On the basis of these findings, Turk ([20]) compared the immunological status of patients with lepromatous leprosy with those showing the Wiskott-Aldrich syndrome. In the light of the present findings it becomes evident that lepromatous leprosy is associated with depression of cell-mediated immunity and diffuse hyperimmunoglobulinemia with a variable deficient response to some antigen but not to others. Thus, the newly emerging immunological status of lepromatous leprosy, an acquired bacterial disease, can be compared to the Wiskott-Aldrich syndrome, which is a primary immunological deficiency state ([2, 9]) in many respects viz: depression of cell-mediated immunity; depletion of small lymphocytes in the paracortical region of lymph nodes; high levels of immunoglobulins IgA and IgM; depressed or missing isoantibodies and increased ASO titer.

SUMMARY

ABO isoagglutinin titer, immunoglobulins, antistreptolysin O titer and the rheumatoid factor were estimated in 40 lepromatous patients. In general, low isoagglutinin titer and absent isoantibodies in 28% of the cases were observed. Quantitative analysis of immunoglobulins showed increased levels of IgM and IgA in these patients. The rheumatoid factor was positive to 1/20 dilution in 35% of the cases, while A.S.O. titer was within the range of 50 to 250 Todd units in 37% and between 333 to 1,250 Todd units in the remaining 63%. Immunoanalysis of these findings indicates that IgM immunoglobulin shows functional dichotomy in these patients. It further suggests that lepromatous leprosy is also associated with diffuse hyperimmunoglobulinemia with dysfunction of blood

group isoagglutinins along with depression of cell-mediated immune responses. It is noted that the newly emerging understanding of the immunological status of these patients can be compared to the Wiskott-Aldrich syndrome in many respects.

RESUMEN

En 40 pacientes lepromatosos se midieron el título de isoaglutinina ABO, las inmunoglobulinas, et título de antiestreptolisina O y el factor reumatoideo. En general, en el 28% de los casos se observó un título bajo de isoaglutinina y falta de isoanticuerpos. El análisis cuantitativo de las inmunoglobulinas mostró niveles aumentados de IgM y de IgA en estos pacientes. El factor reumatoideo fué positivo hasta una dilución de 1/20 en el 35% de los casos, mientras que el título de ASO estaba en el rango de 50 a 250 unidades Todd en el 37% de los casos y entre 333 y 1.250 unidades Todd en el 63% restante. El inmunoanálisis de estos hallazgos indica que la inmunoglobulina IgM en estos pacientes muestra una dicotomía funcional. Sugiere además que la lepra lepromatosa se asocia también con hiperinmunoglobulinemia difusa, con disfunción de las isoaglutininas de los grupos sanguíneos, junto con depresión de las respuestas inmunitarias mediadas por células. Se hace notar que la comprensión del estado inmunológico de estos pacientes, que está emergiendo recientemente, puede compararse en muchos aspectos con el sindrome de Wiskott-Aldrich.

RÉSUMÉ

Chez 40 malades atteints de lèpre lépromateuse, on a déterminé les titres des isoagglutines ABO, des immunoglobulines, de l'antistreptolysine O, et du facteur rhumatoïde. Dans l'ensemble, un titre faible d'isoagglutinines et une déficience en isoanticorps, a été relevé chez 28 pour cent des cas. L'analyse quantitative des immunoglobulines a montré des taux élevé d'IgM et d'IgA chez ces malades. Le facteur rhumatoïde était positif a une dilution de 1/20 chez 35 pour cent des cas, tandis que le titre ASO était situé entre 50 et 250 unités Todd chez 37 pour cent d'entre eux, et entre 333 et 1.250 unités Todd chez les 63 autres pour cent. L'analyse immunologique de ces résultats indique que l'immunoglobuline IgM montre une dichotomie fonctionnelle chez ces malades. Ces résultats suggèrent, en outre, que la lèpre lépromateuse est également associée avec une hyperimmunoglobulinémie diffuse, accompagnée d'un fonctionnement déficient des isoagglutinines pour les groupes sanguins, qui va de paire avec une dépression dans les résponses immunitaires dépendantes des cellules. On constate que l'état immunologique de ces malades, que l'on commence à comprendre depuis peu, peut être à beaucoup d'égards comparé au syndrôme de Wiskott-Aldrich.

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