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Autoantibodies in Leprosy[1]

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During the last three years, while working in Somalia, we have conducted several immunologic investigations in leprosy patients, including skin reactions to tuberculin and other mycobacteria antigens ([9,17,18]) and tests for surface B antigen (HB_sAg) and "e" antigen (HB_e Ag) ([4,10]).

The present work deals with the prevalence of organ-specific and non-organ specific autoantibodies in a random population of patients with lepromatous and tuberculoid forms of leprosy.

MATERIALS AND METHODS

One hundred eighty-six Somalian patients from the Leprosy Hospital in Jilib (south of Mogadishu) were studied. All the patients were classified according to the clinical and histologic criteria of the Ridley-Jopling classification. Only the polar tuberculoid (TT) forms (75 cases) and polar lepromatous (LL) forms (111 cases) were included in the protocol. Sera from healthy Somalian subjects living in the same area were used as controls.

The age of the patients ranged from 16 to 65 years, the mean age being 38 years. The duration of the disease at the time of the study ranged from 2 years to 10 years. All the patients were under treatment with sulfone (DDS) and rifampicin. Patients receiving corticosteroids were excluded from the study.

Autoantibodies directed against thyroid-microsomes, nuclei, smooth muscle, gastric parietal cells and mitochondria were assessed by the classical indirect immunofluorescence technic using 1/10 diluted rabbit antihuman γ-globulin fluorescein isothiocyanate conjugates (DAKO-Immunoglobulins). Sera were tested at the standard 1/10 dilution. Specimens were examined by means of a Leitz "Ortholux" microscope, equipped with a Ploem vertical illuminator.

Thyroglobulin antibodies were assessed by the tanned red cell hemagglutination technic (Wellcome reagents).

Statistical analysis of the results was made by the χ^2 test.

RESULTS

The results obtained are as follows (Table 1 and Fig. 1):

a. *Thyroglobulin antibodies* (*Tg-Abs*) were present in 17 of 111 patients with lepromatous leprosy (15%), and in 16 of 75 patients with the tuberculoid form (20.7%), while they were found in only 7 subjects belonging to the group of healthy controls (5.1%).

b. *Thyroid-microsomal antibodies* (*MF-Abs*) were found in 6 patients with lepromatous leprosy (5.4%), in 4 patients with tuberculoid leprosy (5.3%), and in 3 healthy controls (2.2%).

c. The frequency of *gastric parietal cell antibodies* (*PCA*) in lepromatous patients (2.7%) did not significantly differ from that found in healthy controls (2.9%). No PCA were found in patients with the tuberculoid form of leprosy.

d. An increased frequency of *anti-nuclear antibodies* (*ANA*) was demonstrated; such antibodies were present in 31 of 111 patients with lepromatous leprosy (27.9%), in 21 of 75 patients with tuberculoid leprosy (28.0%), and in only 2 healthy controls (1.4%). The great majority of ANA-containing sera gave a "speckled" pattern of fluorescence.

e. An abnormal frequency of *smooth muscle antibodies* (*SMA*) was also found among leprosy patients. SMA were present in only 9 healthy controls (6.6%) while their frequency was higher among the patients with lepromatous leprosy (31 positive cases or 27.9%) than among patients with tuberculoid leprosy (14 positive cases or 18.6%).

f. Finally, the frequency of *mitochondrial antibodies* (*AMA*) was almost the same in the two groups of leprosy patients. AMA were, in fact, found in 5 subjects with the lepromatous form (4.5%) and in 3 with the tuberculoid

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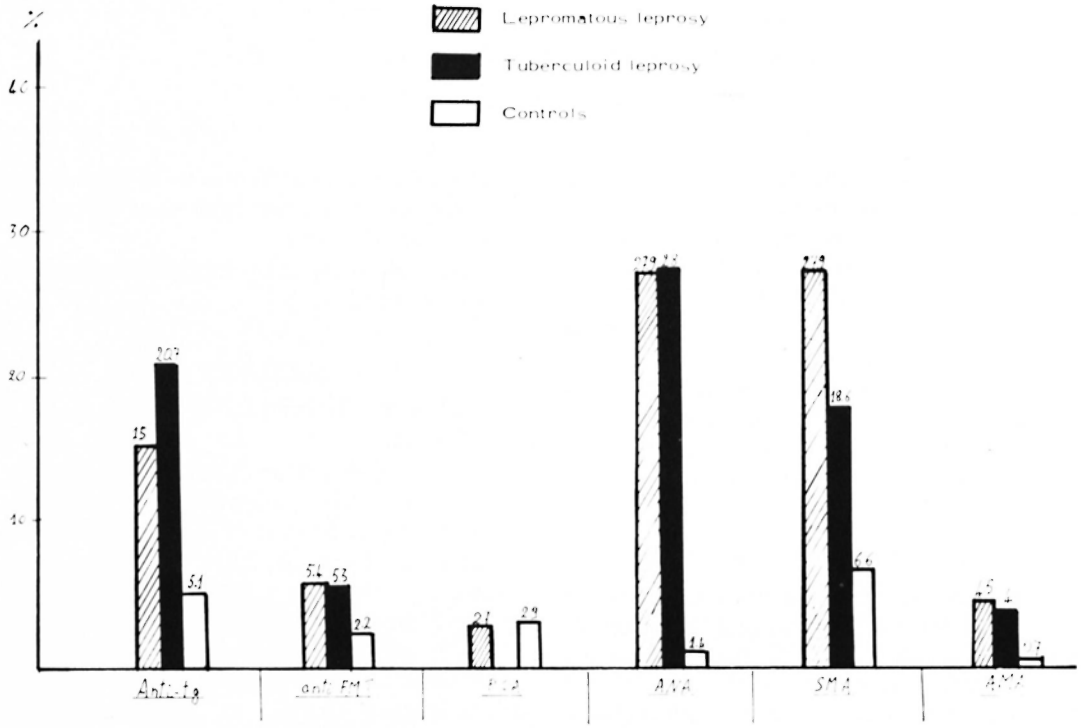
FIG. 1. Incidence of autoantibodies in 111 patients with lepromatous leprosy.



Tg-Abs = antibodies against thyroglobulin.
FM-Abs = antibodies against thyroid-microsomes.
ANA = antibodies against nuclei.
SMA = antibodies against smooth muscle.
AMA = antibodies against mitochondria.
PCA = antibodies against gastric parietal cells.

TABLE 1. *Frequency of autoantibodies in leprosy patients (LL and TT forms) and in matched healthy controls.*

Antibodies against	Controls		LL		TT		Controls
Thyroglobulin	5.1%	$p<0.01$	15.0%	$p<0.01$	20.7%	$p<0.001$	5.1%
Thyroid-microsomes	2.2%	N.S.D.	5.4%	N.S.D.	5.3%	N.S.D.	2.2%
Parietal cells	2.9%	N.S.D.	2.7%	N.S.D.	0	N.S.D.	2.9%
Nuclei	1.4%	$p<0.001$	27.9%	N.S.D.	28.0%	$p<0.001$	1.4%
Smooth muscle	6.6%	$p<0.001$	27.9%	N.S.D.	18.6%	$p<0.01$	6.6%
Mitochondria	0.7%	N.S.D.	4.5%	N.S.D.	4.0%	N.S.D.	0.7%

N.S.D. = no significant difference.

form (4%). Only 1 healthy control showed positive serological reactions for AMA (0.7%).

No significant correlations were found between the frequency of autoantibodies on the one hand and age, sex and duration of the disease on the other.

DISCUSSION

An increased frequency of thyroglobulin antibodies in leprosy was first reported by Bonomo *et al* in 1963 ([1]), and in the following years it has been demonstrated, with a few exceptions ([5,11,13]), that leprosy patients are prone to develop humoral immune responses

TABLE 2. *Frequency (%) of autoantibodies in leprosy patients (LL or TT forms). (Data from literature)*

	anti-TG		ANA		SMA		AMA		PCA	
	LL	TT	LL	TT	LL	TT	LL	TT	LL	TT
Bonomo (1)	42	-	-	-	-	-	-	-	-	-
Matthews (7)	38	-	-	-	-	-	-	-	-	-
Bonomo (2)	48	11	29	-	-	-	-	-	-	-
Malaviya (6)	16	-	26	-	-	-	-	-	-	-
Shwe (15)	16	0	17.8	-	-	-	-	-	-	-
Consigli (3)	-	-	+	-	-	-	-	-	-	-
Petchclai (11)	6.9	0	0	0	-	-	-	-	-	-
Vasquez (20)	-	-	50	-	-	-	-	-	-	-
Wright (21)	0	-	4.2	0	-	-	23.3	-	0	0
Terencio (19)	1.07	-	0	-	3.3	-	7.2	-	-	-
Yantorno (22)	-		54	57	-	-	-	-	-	-
Nelson (8)	-	-	10.7	6.2	-	-	-	-	-	-
Saha (14)	24	9.1	24.4	10	-	-	-	-	-	-
Rea (13)	-	-	13	-	28	-	0	-	9	-
Yumnam (23)	15.3	-	11.5	-	-	-	-	-	-	-

to several autoantigens, including nuclear antigens, IgG determinants, mitochondria and smooth muscle (Table 2).

Most of the above mentioned studies were carried out among patients suffering from the lepromatous form of leprosy. The most widely suggested explanation for the increased frequency of autoantibodies in these patients was that the generalized impairment of cell-mediated immunity in lepromatous leprosy involved also the T-cell subpopulation(s) devoted to the homeostatic control of (auto)immune responses (namely, the suppressor T cells), leading to an increased (auto) antibody production.

The present study confirms previous results concerning the increased frequency of autoantibodies in leprosy and provides direct evidence that the phenomenon is not limited to the lepromatous form of the disease but also extends to the tuberculoid form.

Cell-mediated immune responsiveness has not been as extensively studied in tuberculoid patients, but the current evidence suggests that no generalized impairment occurs among these patients (12). Thus, while the possibility of a suppressor T-cell deficiency cannot be completely excluded, other factors may account for the increased frequency of autoantibodies in both tuberculoid and lepromatous leprosy, including a direct and/or indirect (through the release of lysosomal enzymes by phagocytic cells) tissue damage, an adjuvant-like effect of *M. leprae* (16), a nonspecific stimulation of autoreactive B cells by *M. leprae*, some changes of the molecular configuration of autoantigens induced by the mycobacteria, appearance of previously hidden antigenic determinants as a consequence of the infection and/or induction by *M. leprae* of antibodies cross-reacting with self-antigens.

SUMMARY

The frequency of autoantibodies directed against a variety of tissue constituents (thyroglobulin, thyroid-microsomes, gastric parietal cells, nuclei, smooth muscle, mitochondria) has been assessed in 186 Somalian leprosy patients (living in the leprosy village in Jilib), of whom 111 had lepromatous (LL) leprosy and 75 had the tuberculoid (TT) leprosy, according to the classification of Ridley-Jopling.

A significant increase of thyroglobulin (Tg) antibodies, of antinuclear antibodies (ANA)

and of smooth muscle antibodies (SMA) was found in leprosy patients as compared to matched healthy controls. The frequency of thyroid microsomal antibodies, of gastric parietal cell antibodies and of mitochondrial antibodies in leprosy patients did not significantly differ from that found in the control group.

Autoantibodies occurred to almost the same extent in both tuberculoid (TT) patients and lepromatous (LL) patients; an increased frequency of thyroglobulin antibodies was found among the tuberculoid patients as compared to lepromatous patients while the opposite was found for SMA.

These results seem to indicate that the hypothesis of a suppressor T cell deficiency leading to an increased autoantibody production in leprosy is too simplistic and that other mechanisms may account for the increased autoantibody production in both the tuberculoid and lepromatous forms.

RESUMEN

Se estudió la frecuencia de autoanticuerpos dirigidos contra una variedad de constituyentes tisulares (tiroglobulina, microsomas tiroideos, células gástricas parietales, núcleos, músculo liso y mitocondrias) en 186 personas de Somalia con lepra (habitantes del leprosario en Jilib). De estos pacientes, 111 tenian lepra lepromatosa y 75 tenian lepra tuberculoide, según, la clasificación de Ridley-Jopling.

Comparando con controles sanos, en los pacientes con lepra se encontró un incremento importante de anticuerpos anti-tiroglubulina, antinucleares (ANA) y anti-músculo liso (AML). La frecuencia de anticuerpos contra microsomas tiroideos, contra células gástricas parietales y contra mitocondrias, no difirió significativamente de la encontrada en el grupo control.

Se encontraron autoanticuerpos cási con la misma frecuencia tanto en los pacientes tuberculoides TT como en los lepromatosos LL. Sin embargo, los pacientes tuberculoides tuvieron una mayor frecuencia de anticuerpos contra tiroglobulina que los lepromatosos pero una menor frecuencia de anticuerpos contra músculo liso (AML).

Estos resultados parecen indicar que la hipótesis de que una deficiencia en células T supresoras conduce a la incrementada producción de autoanticuerpos en lepra, es muy simplista y que otros mecanismos pueden explicar tal sobreproducción de autoanticuerpos en ambas formas de lepra, tuberculoide y lepromatosa.

RÉSUMÉ

Chez 186 malades somaliens, vivant près du village pour malades de Jilib, on a étudié la fréquence des anticorps contre une variété de constituants tissularies (thyroglobuline, microsomes thyroïdiens, cellules pariétales gastriques, noyaux, muscles lisses, mitochondries). Parmi ces malades, 111 étaient atteints de lèpre lépromateuse LL, et 75 souffraient d'une lèpre tuberculoïde TT, selon la classification de Ridley-Jopling.

Chez les malades de la lèpre, par rapport à des témoins sains assortis de manière appropriée, on a observé une augmentation significative des anticorps contre la thyroglubuline Tg, des anticorps anti-nucléaires (ANA), et des anticorps contre les muscles lisses (SMA). Par contre, la fréquence des anticorps microsomiques thyroïdiens, des anticorps contre les cellules pariétales gastriques, et des anticorps mitochondriens, n'a pas montré de différence significative chez les malades de la lèpre, par rapport aux groupes témoins.

On a constaté que la fréquence des autoanticorps était à peu près similaire chez les malades tuberculoïdes TT et chez les malades lépromateux LL. Une fréquence accrue d'anticorps thyroglobuline a été observée chez les malades tuberculoïdes, par comparaison avec les malades lépromateux; une observation opposée a été faite concernant les anticorps SMA.

Ces résultats paraissent indiquer que l'hypothèse d'une déficience en cellules supressives T, menant à une production accrue d'auto-anticorps dans la lèpre, est par trop élémentaire. D'autres mécanismes doivent intervenir pour entraîner une production accrue d'auto-anticorps, tant dans la forme tuberculoïde que dans la forme lépromateuse de la lèpre.

REFERENCES

1. Bonomo, L. Dammacco, F., Pinto, L. and Barbieri, G. Thyroglobulin antibodies in leprosy. Lancet **2** (1963) 807-809.
2. Bonomo, L., Tursi, A., Trimigliozzi, G. and Dammacco, F. L.E. cells and antinuclear factors in leprosy. Br. Med. J. **2** (1965) 689-690.
3. Consigli, C. A., Yantorno, C. E., Vasquez, C. A. and Riera, C. N. Reacciones de anticuerpos séricos en grupos familiares con enfermos de lepra. Leprologica **18** (1973) 275-276.
4. Delia, S., Nuti, M. and Soro, S. Rapporti tra HB_sAg e parassitosi: osservazioni in pazienti con anchilostomiasi e con schistosomiasi. Quad. Sclavo. Diagn. **13** (1977) 238-243.
5. Dhople, A. M. Possible autoimmune phenomenon in leprosy. Japan J. Exp. Med. **42** (1972) 125-129.
6. Malaviya, A. N., Pasricha, A., Pasricha, J. S. and Mehta, J. S. Significance of serologic

abnormalities in lepromatous leprosy. Int. J. Lepr. **40** (1972) 361-365.

7. MATTHEWS, L. J. and TRAUTMAN, J. R. Clinical and serological profiles in leprosy. Lancet **2** (1965) 915-918.
8. NELSON, D. S., PENROSE, J. M., WATERS, M. F. R., PEARSON, J. M. H. and NELSON, M. Depressive effect of serum from patients with leprosy on mixed lymphocyte reactions. Influence of antileprosy treatment. Clin. Exp. Immunol. **22** (1975) 385-392.
9. NUTI, M. TARABINI, C. G. and TARABINI, C. G. L. Lebbra e mycobatteri atipici. 1) Studio della cutireattività a varie sensitine atipiche in pazienti portaori di lebbra lepromatosa e tuberculoide. Acta Leprol. **68** (1977) 25-34.
10. NUTI, M., TARABINI, C. G., TARABINI, C. G. L. and THAMER, G. L'antigene "e" (HBeAg) nella lebbra. Quad. Sclavo. Diagn. **13** (1977) 393-403.
11. PETCHCLAI, B., CHUTHANONDH, R., RUNGRUONG, S. and RAMASOOTA, T. Autoantibodies in leprosy among Thai patients. Lancet **1** (1973) 1481-1482.
12. REA, T. H. and LEVAN, N. E. Current concepts in the immunology of leprosy. Arch. Dermatol. **113** (1977) 345-352.
13. REA, T. H., QUISMORIO, F. P., HARDING, B., NIES, K. M., DI SAIA, P. J., LEVAN, N. E. and FRIOU, G. J. Immunologic responses in patients with lepromatous leprosy. Arch. Dermatol. **112** (1976) 791-800.
14. SAHA, K., DUTTA, R. N. and MITTAL, M. M. Immunologic aspects of leprosy as related to leucocytic isoantibodies and platelet aggregating factors. Int. J. Lepr. **43** (1975) 239-248.
15. SHWE, T. Clinical significance of autoimmune antibodies in leprosy. Trans. R. Soc. Trop. Med. Hyg. **66** (1972) 749-753.
16. STEWART-TULL, D. E. S., SHIMONO, T., KOTANI, S. KATO, M., OGAWA, Y., YAMAMURA, Y., KOGA, T. and PEARSON, C. M. The adjuvant activity of a nontoxic water-soluble glycopeptide present in large quantities in the culture filtrate of *Mycobacterium tuberculosis* strain DT. Immunology **29** (1975) 1-15.
17. TARABINI, C. G., NUTI, M. and TARABINI, C. G. L. Lebbra e mycobatteri atipici. 2) Studio sulle lebbroreazioni provocate da sensitine tubercolari tipiche ed atipiche in casi di lebbra lepromatosa. Acta. Leprol. **68** (1977) 35-43.
18. TARABINI, C. G., TARABINI, C. G. L. and NUTI, M. Lebbra e mycobatteri atipici. 3) Studio del trattamento delle lebbroreazioni da sensitine tubercolari tipiche ed atipiche in pazienti con lebbra lepromatosa. Acta. Leprol. **68** (1977) 45-52.
19. TERENCIO DE LAS AGUAS, J., RICHERI, D. and ALEMANY, A. M. Estudio de la immunidad humoral en la lepra. Rev. Leprol Fontilles **9** (1974) 355-363.
20. VASQUEZ, C. A., RIERA, C. M. and YANTORNO, C. Respuesta humoral auto e heteroinmune en lepra. Rev. Leprol. Fontilles **9** (1973) 151-161.
21. WRIGHT, D. J. M. Autoantibodies in leprosy. Lancet **2** (1973) 40.
22. YANTORNO, C. E., VASQUEZ, C. A. and RIERA, C. M. Reaciones anomalas auto y heteroinmunes en enfermos hansenianos y convivientes clinicamente sanos. Rev. Leprol. Fontilles **9** (1974) 471-482.
23. YUMNAM, I. S., SEHGAL, S., KAUR, S., KUMAR, B. and RASTOGI, G. K. Evaluation of thyroid functions in leprosy. III. Circulating auto-antibodies against thyroid and nuclear components. Lepr. India **49** 495-499.