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A Comparative Study of Testicular Involvement in Lepromatous and Borderline Lepromatous Leprosy[1]

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Testicular anatomical changes in leprosy ([3–5, 11]) and the secondary problems of sterility and androgen deficiency are well recognized phenomena ([1, 3–6, 8, 9, 11, 14, 16]). The pathogenesis of testicular involvement is probably hematogenesis dissemination of *Mycobacterium leprae* to endothelial cells followed by interstitial infiltration, tubular atrophy, and fibrosis ([3, 4, 11]), but the possibility of immunological injury has been suggested ([20]). Although testicular involvement appears to be common only in the more severe forms of the disease, the Ridley system ([15]) of classification did not exist when some of the benchmark anatomical studies were executed ([3, 5, 11]), was not used in most of the functional studies reported ([1, 6, 8, 9, 16]) or, if used ([14]), potentially important distinctions between borderline lepromatous (BL) and lepromatous (LL) patients were not made.

Testicular involvement in leprosy has been addressed by anatomical studies ([3–5, 11]), semen analysis ([4, 16]), and serological techniques ([1, 6, 8, 9, 14, 16]). The latter, involving only phlebotomy and being otherwise neither invasive nor demanding upon the patient, are easily performed and well suited to the survey of large numbers of subjects.

In adult men, elevated serum follicle stimulating hormone (FSH) levels indicate seminiferous tubule injury; decreased inhibin production by Sertoli cells releases feed-back inhibition upon FSH production. Elevated leutenizing hormone (LH) levels indicate Leydig cell (interstitial) injury; decreased testosterone production releases feed-back inhibition upon LH production. If sufficient Leydig cells are present, the increase in LH leads to a compensatory synthesis of testosterone by the remaining Leydig cells; with insufficient Leydig cells, androgen deficiency results.

In an attempt to define the prevalence rates of testicular involvement and androgen deficiency in our clinic population, a study of serum gonotrophins and testosterone levels was performed. The finding of the comparative sparing of BL and the heavy involvement of LL patients, as reported here, may be of practical importance, indicating a utility for the Ridley system in nonimmunological matters and suggesting

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that osteoporosis might be a common, but treatable, sequella of LL disease in men.

MATERIALS AND METHODS

Patients were randomly chosen for study at the time of a routinely scheduled visit to the Hansen's Disease Clinic of the Los Angeles County/University of Southern California Medical Center. Those eligible were men from 18 through 65 years of age whose pretreatment skin biopsy had been classified by the author using Ridley's criteria ([15]); the original classification was used in the report, although possibly inconsistent instances were reviewed. Patients with obvious gynecomastia were excluded, but, as in the study by Ree, *et al.* ([14]), no other clinical signs relating to endocrine status were sought. All phlebotomies were performed between 8:30 and 11:00 a.m. Serum was routinely saved and stored at −20°C.

Total serum testosterone was determined by a double-antibody radioimmunoassay method ([17]), using the Pantex Immunotestosterone Direct Kit. FSH and LH were determined by double-antibody radioimmunoassay ([18]), using Serano's Rapid FSH Kit and Rapid LH Kit.

In eight BL and 17 LL subjects with low-normal total testosterone values, free serum testosterone levels were measured on an aliquot of banked serum. Measurement was made at the Nichols Institute, San Juan Capistrano, California, U.S.A., using the method of Vermuelen, *et al.* ([19]).

The normal values for FSH (2.0–10.0 mIU/ml) and LH (4.9–15.0 mIU/ml) were those established by the manufacturer. The normal range for total serum testosterone (280–1000 ng/dl [16]) was that recommended by Dr. Richard Horton (personal communication). The normal range for free serum testosterone (50–210 pg/ml) was that previously established by the Nichols Institute.

Statistical analysis was performed using the CLINFO program at the Clinical Research Center (supported by GCRC RR-43) of the Los Angeles County/University of Southern California Medical Center. If population distribution was normal, as suggested by the normality test of Wilk-Shapiro, means were compared by the *t* test; if not normal, populations were compared by the Wilcoxon rank sum test. Regression analysis used the least-squares linear regression method. Chi-squared analysis utilized the Yates' correction.

RESULTS

The results are summarized in Table 1. Forty-two lepromatous and 21 borderline lepromatous patients were studied and appeared to be comparable in regard to age at the time of study, age at the onset of symptoms, age at the onset of treatment, duration of symptomatic disease, and the time elapsing between the onset of symptoms and the beginning of treatment. The mean duration of treatment was insignificantly larger in the LL group, 6.1 years, than in the BL subjects, 3.8, but the median value, 3 years, was the same in both.

Concerning serum FSH values, a measure of tubular involvement, 4 of 21 (19%) BL and 36 of 42 (86%) LL patients had FSH levels greater than 10 mIU/ml. The BL patients had mean FSH levels of 10.5 and LL of 40.9 mIU/ml. Although both mean values are above the upper limits of normal, the mean values differed significantly from each other ($p < 0.0001$).

Concerning serum LH values, a measure of Leydig cell involvement, 2 of 21 (10%) BL and 33 of 42 (79%) LL patients had values above 15 mIU/ml. The mean value for BL patients, 11.3, was within normal limits and differed significantly ($p < 0.0001$) from that of LL patients, 32.5 mIU/ml.

Using 280 ng/dl as the lower limit of normal for serum total testosterone values, none of the 21 BL patients was determined to be androgen deficient but 13 of 42 (31%) LL patients were. Of the 8 BL and 17 LL patients in the low-normal serum testosterone levels in which serum free testosterone was determined, one BL subject was identified as being androgen deficient, i.e., values less than 50 pg/ml, and an additional 5 LL patients were so designated. Thus, using either serum total testosterone or serum free testosterone levels to define androgen deficiency, 1 of 21 (5%) BL and 18 of 42 (43%) were androgen deficient and this difference was significant ($p < 0.01$) by chi-squared analysis. In comparing mean values of serum total testosterone, BL patients, 492.3,

TABLE 1. *Summary of demographic and endocrinologic data.*

	Borderline lepromatous (BL) N = 12		Statistical significance	Lepromatous (LL) N = 42	
	Mean ± S.D.	Median (low–high)	*t*, Z, or χ^2 p value	Mean ± S.D.	Median (low–high)
Age at time of study	37.9 ± 9.6	39 (21–55)	NS[a]	39.0 ± 10.4	36 (23–64)
Age at symptom onset	31.5 ± 8.1	32 (16–44)	NS	30.8 ± 9.6	30 (19–57)
Age at onset of treatment	34.0 ± 9.4	32 (17–48)	NS	33.1 ± 9.8	30 (19–59)
Duration of symptomatic disease	6.4 ± 4.2	5 (1–16)	NS	8.3 ± 8	5 (1–34)
Duration of treatment	3.8 ± 3.7	3 (0–14)	NS	6.1 ± 7.5 2.3 ± 2.6	3 (0–33)
Time between onset and treatment initiation	2.6 ± 2.6	1 (0.1–8)	NS	2.3 ± 2.6	1 (0.3–12)
FSH in mIU/ml	10.5 ± 12.0	7 (3–53)	$Z = -4.918$ $p < 0.0001$	40.9 ± 33.2	35 (5–148)
LH in mIU/ml	11.3 ± 8.8	10 (4–40)	$Z = -5.312$ $p < 0.0001$	32.5 ± 18.4	31 (6–85)
Total/testerone ng/dl	492 ± 129.7	493 (296–711)	$t = 4.1$ $p < 0.0001$	344.9 ± 137.1	348 (10–643)
No. hypogonadal	1		$\chi^2 = 7.8$ $p < 0.01$	18	

[a] NS = not statistically significant.

were significantly higher ($p < 0.0001$) than LL patients, 344.9 ng/dl.

In using regression analysis, FSH, LH, and total testosterone values were not associated in a significant way, either positively or negatively, with any of the first six variables listed in Table 1 in either LL or BL patients (data not shown). Also, when LL patients were subdivided into 18 androgen-deficient and 24 nonandrogen-deficient subjects, the two subgroups did not differ from one another concerning any of the first six variables listed in Table 1. Finally, among lepromatous subjects no subgroup could be identified on the basis of polar vs subpolar lepromatous disease or presentation with erythema nodosum leprosum or the Lucio reaction.

The anticipated inverse association between serum total testosterone and LH levels was weak in BL patients ($r = -0.31$) and was of doubtful significance in LL patients ($r = -0.34$, $p = 0.033$). However, stronger inverse correlations were seen when comparing LH values with free testosterone values in both BL ($r = -0.62$) and LL ($r = -0.61$) subjects. A positive correlation between FSH and LH levels was observed in both BL and LL groups: $r = 0.90$, $p < 0.001$ and $r = 0.71$, $p < 0.0001$, respectively.

The BL and LL groups did differ in ethnic composition (Table 2). For example, Mexican-born patients comprised 48% of the BL but 80% of the LL group. In contrast, individuals from Southeast Asia were 24% of the BL but 12% of the LL group. These differences in distribution probably reflect both the random method of selecting sub-

TABLE 2. *Distribution of patients by place of birth.*

	Borderline lepromatous (BL)	Lepromatous (LL)
Mexico	10	34
Samoa	1	0
The Philippines	4	2
Southeast Asia	5	5
India	1	0
Puerto Rico	0	1
Total	21	42

jects and the differences in distribution of the various types of leprosy among different ethnic groups ([10]). Because 4 of the 5 (80%) LL patients from Southeast Asia had elevated FSH and LH values and 2 (40%) were androgen deficient, i.e., prevalence rates similar to the entire LL group, it is unlikely that ethnic composition influenced the results in the LL patients. However, in the BL group the sole androgen-deficient patient was Mexican-born, as were the only two with elevated LH values and as were 3 of the 4 with elevated FSH levels. Thus, 6 of the 7 abnormal bits of data in the BL group were found in the Mexican-born patients.

DISCUSSION

The most important finding in this study is the high prevalence of testicular involvement in lepromatous disease as judged by elevated FSH and LH values and the high prevalence of decreased total or free serum testosterone levels. That testicular involvement in leprosy is common in multibacillary disease has been well established by previous studies ([1, 3–6, 8, 9, 11, 14, 16]). The present investigation demonstrates that testicular involvement is a particular burden among LL patients, and that BL patients, although by no means spared, have a statistically significantly lesser degree of testicular involvement.

There are two important corollaries to these findings. For leprology, the Ridley system of classification, when used to distinguish between BL and LL, is not only assigning a semiquantitative degree of resistance to bacillary proliferation ([15]), but is indicating a high or low risk for perceptible testicular involvement. For clinical care the high prevalence of gonadal failure suggests that osteoporosis might be yet another serious medical problem to be borne by the LL patient but, and of particular importance, one that could be prevented by replacement therapy.

In either the BL or the LL population, FSH, LH, and serum total testosterone levels could not be associated with age at the time of study, age at onset of first symptoms, age at onset of treatment, disease duration, duration of treatment, or the time interval between the onset of symptoms and the beginning of treatment. This failure to find an association is consistent with a number of not mutually exclusive considerations: a) A greater degree of bacillemia in LL than in BL would permit more widespread disease in LL, including testicular involvement. b) The greater degree of resistance in BL would produce a shorter time span between disease onset and symptom onset, thus allowing less widespread disease. c) Among lepromatous patients, testicular involvement probably occurs early in the course of the disease and well before the onset of symptoms.

The present study is not, nor was it intended to be, exhaustive. Several questions were not addressed. For example, the high prevalence of FSH values would suggest a higher incidence of hypospermia or azospermia in LL than in BL patients, but no attempt was made to do sperm counts. Also, the incidence of subclinical testicular involvement in those individuals with normal endocrine values is of interest, and may well be common, but the question was not considered to be of sufficient moment to justify testicular biopsies in asymptomatic individuals. Finally, patients were not screened to determine the prevalence of infertility or sexual malfunction as clinical problems putatively secondary to testicular involvement.

As should be the case, this study raises new questions but, because of its limitations, does not answer them. What is the prevalence of osteoporosis, as judged by decreased bone density, in men with lepromatous leprosy and how early in the disease course can such changes be identified? Will the LL patients with normal values develop abnormal values with the passage of time despite adequate antibacillary therapy? Is the evident sparing of non-Mexican men with BL disease attributable to a sampling error or is the Mexican predilection real, another ethnic-associated manifestation of Hansen's disease in addition to, for example, the Lucio reaction ([13])? With such striking endocrine differences between BL and LL subjects, one becomes very curious as to what the magnitude of interobserver differences will prove to be when experts read BL and LL biopsy specimens ([2]).

The observed negative correlation between LH and total serum testosterone was weaker than reported by some ([14]), specifi-

cally −0.48 (p = 0.01) in BL and LL taken together, −0.34 (p = 0.03) in LL and −0.31 (p = 0.17) in BL. However, a stronger negative correlation was observed between LH and serum free testosterone values, specifically −0.67 (p = 0.001) in BL and LL taken together, −0.61 (p = 0.01) in LL and −0.62 in BL (p = 0.09). The hyperglobulinemia often present in multibacillary patients ([12]) could lead to increased serum-bound testosterone without influencing free testosterone values, thus explaining the poor correlation between total testosterone and LH. That 5 of 17 LL patients with low-normal total serum testosterone levels were found to have abnormally low free testosterone values is consistent with this explanation.

Our results appear to be contrary to the findings of others ([14, 16]), and to the general rule that with diffuse injury to the testicle tubular damage occurs first and interstitial damage is a later event. For example, of the 42 LL subjects 34 had elevated levels of both FSH and LH, 6 had normal levels of both, and only 2 showed mild FSH elevations (13–14 mIU/ml) in the presence of normal LH values. These contrary data are probably more apparent than real. These LL patients are predominantly Mexican-born, a group in whom diffuse non-nodular disease is common, a circumstance which probably prolongs the time interval between disease (and bacillemia) onset and the appearance of symptoms. Thus, testicular involvement is likely to be an early event in the natural history of the illness and is far advanced, i.e., showing both tubular and interstitial change, by the time leprosy symptoms occur.

SUMMARY

To measure the comparative prevalence of testicular involvement in borderline lepromatous (BL) and lepromatous (LL) leprosy patients, serum FSH, LH, and total testosterone levels were measured in 42 LL and 21 BL subjects. Serum FSH levels were elevated in 19% of BL and in 86% of LL patients. Serum LH values were increased in 10% of BL and in 79% of LL patients. Total serum testosterone values below the normal limit of 280 ng/dl were not found in BL subjects but were present in 31% (13) of the LL cases. By measuring serum free testosterone in patients with low-normal total values, one BL and an additional five LL patients could be identified as below normal limits, i.e., <50 pg/ml. Thus, androgen deficiency was present in 5% of BL and in 43% of LL subjects. All of these differences between the BL and LL patients were statistically significant.

RESUMEN

Para medir la prevalencia comparativa de la afectación testicular en la lepra lepromatosa limítrofe (BL) y en la lepra lepromatosa polar (LL), se midieron los niveles séricos de FSH, LH y testosterona total, en 42 pacientes LL y en 21 pacientes BL. Los niveles séricos de FSH se encontraron elevados en el 19% de los pacientes BL y en el 86% de los pacientes LL. Los niveles séricos de LH estuvieron aumentados en el 10% des los casos BL y en el 79% de los LL. No se encontraron valores de testosterona total por abajo del límite normal de 280 ng/dl en los sujetos BL pero sí en el 31% (13) de los casos LL. Midiendo los niveles de testosterona libre en suero de los pacientes con valores totales normales bajos, se pudieron identificar un paciente BL y 5 pacientes LL adicionales con valores por abajo de los límites normales (menos de 50 pg/ml). Así, la deficiencia en andrógenos estuvo presente en el 5% de los pacientes BL y en el 43% de los individuos LL. Todas estas diferencias entre los pacientes BL y LL fueron estadísticamente significativas.

RÉSUMÉ

En vue de mesurer la prévalence comparée de l'atteinte testiculaire chez les malades de la lèpre atteints respectivement de lèpre dimorphe (BL) et lépromateuse (LL), on a procédé à des mesures des taux de FSH sérique, de LH, et de testosterone totale chez 42 malades LL et chez 21 malades BL. Les taux sériques de FSH étaient augmentés chez 19% des malades BL, et chez 86% des malades LL. Les valeurs de la LH sérique étaient augmentées chez 10% des malades BL et chez 79% des malades LL. Les valeurs totales de la testosterone sérique étaient en deçà des limites normales de 280 ng/dl chez 31% des cas LL, alors qu'aucune diminution n'a été trouvée chez les individus BL. Lorsque l'on mesure les valeurs de la testosterone libre du sérum chez des malades présentant des valeurs totales en-dessous la normale, on constate qu' 1 malade BL, et 5 malades LL pouvaient être identifiés comme présentant des valeurs infra-normales, soit <50 pg/ml. Dès lors, on peut en conclure qu'une insuffisance en androgènes était présente chez 5% des malades BL et chez 43% des sujets LL. Toutes ces différences entre les malades BL et LL étaient statistiquement significatives.

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REFERENCES

1. DASH, R. J., SAMUEL, E., KAUR, S., DATTA, B. N. and RASTOGI, G. K. Evaluation of male gonadal function in leprosy. Horm. Metab. Res. **10** (1978) 362.
2. FINE, P. E. M., JOB, C. K., MCDOUGALL, A. C., MEYERS, W. M. and PONNIGHAUS, J. M. Comparability among histopathologists in the diagnosis and classification of lesions suspected of leprosy in Malawi. Int. J. Lepr. **54** (1986) 614–625.
3. GRABSTALD, H. and SWAN, L. L. Genitourinary lesions in leprosy with special reference to the problem of atrophy of the testes. JAMA **149** (1952) 1287–1291.
4. IBRAHIEM, A. A., AWAD, H. A., METAWI, B. A. and HAMADA, T. A. Y. Pathologic changes in testis and epididymis of infertile leprotic males. Int. J. Lepr. **47** (1979) 44–49.
5. JOB, C. K. Gynecomastia and leprous orchitis, a preliminary study. Int. J. Lepr. **29** (1961) 423–441.
6. KANNAN, V. and VIJAYA, G. Endocrine testicular functions in leprosy. Horm. Metabol. Res. **16** (1984) 146–150.
7. KINOUCHI, T., PAGES, L. and HORTON, R. A specific radioimmunoassay for testosterone in peripheral plasma. J. Lab. Clin. Med. **82** (1973) 309–316.
8. MARTIN, F. I. R., MADDOCKS, I., BROWN, J. B. and HUDSON, B. Leprous endocrinopathy. Lancet **2** (1968) 1320–1321.
9. MORELY, J. E., DISTILLER, L. A., SAGEL, J., KOK, S. H., KAY, G., CARR, P. and KATZ, M. Hormonal changes associated with testicular atrophy and gynecomastia in patients with leprosy. Clin. Endocrinol. **6** (1977) 299–303.
10. NEWALL, K. W. An epidemiologist's view of leprosy. Bull. WHO **34** (1966) 827–857.
11. POWELL, C. S. and SWANN, L. L. Leprosy: pathology changes observed in fifty consecutive necropsies. Am. J. Pathol. **31** (1955) 1131–1147.
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. and LEVAN, N. E. Lucio's phenomenon and diffuse non-nodular lepromatous leprosy. Arch. Dermatol. **114** (1978) 1023–1028.
14. REE, G. H., MARTIN, F. I. R., MYLES, K. and PELUSO, I. Hormonal changes in human leprosy. Lepr. Rev. **52** (1981) 121–126.
15. RIDLEY, D. S. Histological classification and the immunological spectrum of leprosy. Bull. WHO **51** (1974) 451–465.
16. SHILO, S., LIVSHIN, Y., SHESKIN, J. and SPITZ, I. M. Gonadal function in lepromatous leprosy. Lepr. Rev. **52** (1981) 127–134.
17. TEITZ, N. *Fundamentals of Clinical Chemistry.* 2nd ed. Philadelphia: W. B. Saunders, 1970.
18. *Textbook of Endocrinology.* Williams, R. H., ed. 6th ed. Philadelphia: W. B. Saunders, 1981.
19. VERMUELEN, A., STOICA, A. and VENDONCK, L. The apparent free testosterone concentration: an index of androgenicity. J. Clin. Endocrinol. **33** (1971) 759–767.
20. WALL, J. R. and WRIGHT, D. J. M. Antibodies against testicular germinal cells in lepromatous leprosy. Clin. Exp. Immunol. **17** (1974) 51–59.