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Testicular dysfunction in leprosy: relationships of FSH, LH and testosterone to disease classification, activity and duration

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Summary Luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone levels were determined by radioimmunoassay (RIA) in leprosy patients and analysed for effect of disease classification, disease activity and duration of disease. LH and FSH levels were found to be significantly elevated in lepromatous patients compared to borderline–lepromatous, midborderline and borderline–tuberculoid patients. A positive correlation was seen between LH and FSH and a negative correlation was seen between testosterone and both LH and FSH. No correlation was seen between hormone levels and measures of disease activity: bacillary index and IgM to phenolic glycolipid I, a *Mycobacterium leprae* antigen. A significant correlation was seen between duration of disease and FSH when age was taken into account, indicating that testicular dysfunction is probably cumulative and irreversible. It is recommended that LL patients be routinely screened for hypogonadism using FSH, LH and testosterone levels.

Introduction

The testes are known to be a favoured site for focal damage in patients with leprosy. This is probably because bacillary growth is favoured at the lower temperature in the scrotum since *Mycobacterium leprae* grow optimally at about 30°C.[1] In spite of this, there are few studies of testicular disease in men with proven leprosy. We, therefore, thought it pertinent to examine men for evidence of testicular failure who are under treatment for leprosy. In the current study, 93 men classified according to the Ridley–Jopling system[2] were evaluated for FSH, LH, and testosterone levels, and the findings were correlated with bacillary index (BI) and IgM antibody to the phenolic glycolipid I (PGL-I), an *M. leprae* specific antigen. The results, indicating that hypogonadism is a primary manifestation of lepromatous leprosy are the subject of this report.

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Materials and methods

PATIENTS

Ninety-three male leprosy patients receiving treatment at the New York City Regional Hansen's Disease Program were clinically and histologically classified by the Ridley–Jopling scale[2] as follows: LL, lepromatous leprosy ($n=55$); BL, borderline lepromatous ($n=9$); BB, midborderline ($n=7$); BT borderline–tuberculoid leprosy ($n=22$). The BI, an estimation of the total bacillary load in leprosy patients, was measured on a semiquantitative scale (0 to 6+)[3] approximating that of Ridley.[4] Histology and BI were determined from skin punch biopsies at the Gillis W Long Hansen's Disease Center, Carville, LA. Serum samples were collected from leprosy patients and stored in aliquots at −70°C for antibody testing.

ELISA FOR SERUM ANTIBODIES TO PGL-1

IgM antibodies to the phenolic glycolipid I (PGL-I) antigen of *M. leprae* were detected by enzyme-linked immunosorbent assay as previously described.[5,6] PGL-I was incorporated into liposomes with sphingomyelin, cholesterol, and dicetyl phosphate. Control liposomes were made without PGL-I.

RADIOIMMUNOASSAY (RIA) FOR SERUM HORMONE LEVELS

Determination of serum LH and FSH level was done by RIA with commercially available kits (Corning Medical; Medfield, MA). The RIA for LH had a detection limit of 0·9 mIU/ml. The RIA for FSH had a detection limit of 1 mIU/ml. RIA for testosterone was performed with a kit from Diagnostic Products Corp., Los Angeles, Ca. RIA for testosterone had a detection limit of 0·11 ng/dl. Cross-reactivity of testosterone assay was less than 10% with dihydrotestosterone and much less with other androgens.

STATISTICAL ANALYSES

Statistical analyses were performed using the BMDP package. Analysis of variance was performed with patients divided into Ridley–Jopling classes and levels of significance calculated by the Bonferonni test to determine the effect of disease classification on BI, antiPGL-I IgM and hormone levels. Correlation coefficients were calculated to examine relationships between BI, antiPGL-I IGM and hormone levels. To examine the effect of duration of disease on hormone levels a subgroup of 16 recently diagnosed patients (<2 years) was analysed separately. In addition partial correlation analysis was performed on hormone levels, duration of disease, and age to determine if duration of disease had any effect on hormone levels, independent of age.

Results

TESTOSTERONE AND GONADOTROPIN LEVELS IN PATIENTS WITH LEPROSY

Nineteen of the patients examined had testosterone levels below the lower limit of normal for men (less than 300 ng/dl). In 4 out of 19, these low levels occurred without an elevation in LH or FSH. All 4 of these low testosterone normal FSH-LH patients were non-LL (2BT, 1BB, 1BL), while the remaining 15 low testosterone patients with elevated FSH and/or LH were all LL. The 4 non-LL low testosterone patients had testosterone levels that were significantly higher than the 15 LL low testosterone patients (mean testosterone ± SD: 284 ± 14 *vs* 143 ± 73, $p<0{\cdot}005$). In addition, LH and FSH levels were elevated in 31 and 32 of the total patient population, respectively. Thus, approximately one-third of the men with the diagnosis of leprosy had evidence of hypogonadism when only a single blood sample was used for hormone measurements.

Since testosterone regulates the secretion of LH, there is a clear causative relationship between a decrease in testosterone and a rise in LH. We, therefore, examined the relationship between testosterone and LH in patients with leprosy (Figure 1(a). There was a significant negative correlation between testosterone and LH ($r=0{\cdot}41$, $p<0{\cdot}001$). It was of interest to note, however,

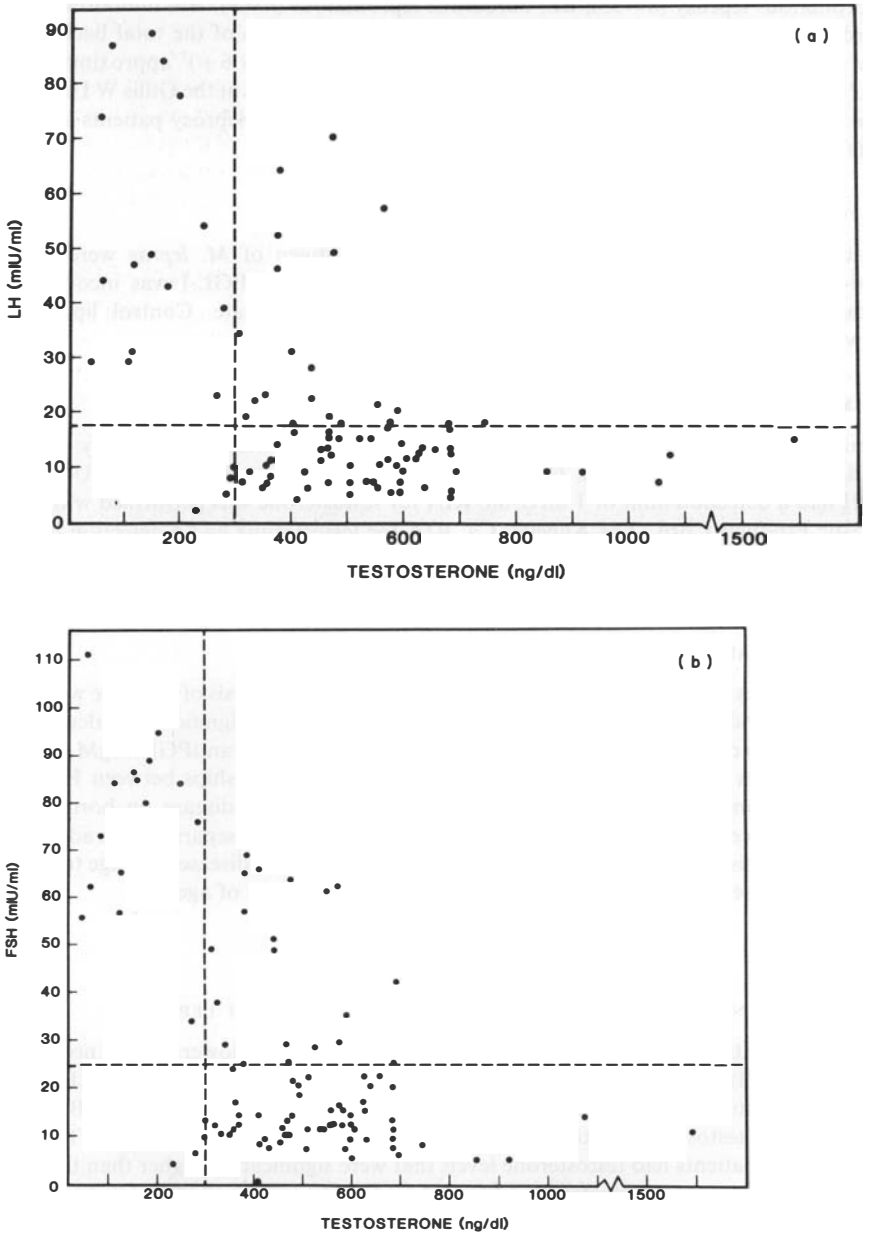

Figure 1(a). Testosterone *vs* luteinizing hormone (LH) for all leprosy patients ($r=-0{\cdot}41$, $p<0{\cdot}001$). (b) Testosterone *vs* follicle-stimulating hormone (FSH) for all leprosy patients ($r=0{\cdot}48$, $p<0{\cdot}001$).

that in 16 out of 31 individuals the elevation of LH occurred in association with a normal testosterone level suggesting that in spite of the altered Leydig cell function, testosterone secretion could still be increased in response to an elevation of LH such that testosterone secretion was maintained in a compensated state. By contrast, in 15 out of 31 individuals testosterone secretion could not be compensated by an elevated LH level.

Even though testosterone does not reciprocally regulate FSH secretion, there was also a negative correlation between this hormone and testosterone ($r = -0{\cdot}48$, $p < 0{\cdot}001$). This relationship is shown in Figure 1b. Since FSH increases as the seminiferous tubules are damaged, FSH should correlate inversely with testosterone only if damage to Leydig cells occurs concomitantly with that to tubules. As a rise in LH is the best index of abnormal Leydig cell function, the levels of this hormone were compared with those for FSH. The LH and FSH levels for the entire study population were significantly correlated ($r = 0{\cdot}82$, $p < 0{\cdot}001$) (Figure 2) and were even more strongly correlated for the newly diagnosed individuals ($r = 0{\cdot}95$, $p < 0{\cdot}001$, data not shown).

THE RELATIONSHIP BETWEEN HYPOGONADISM AND THE DISEASE STATE

LH levels are shown as a function of disease classification in Figure 3. LH and FSH levels were elevated in one-half of patients with LL (27 out of 55 for LH (Figure 3); 29 out of 55 for FSH, data not shown) and in only 10% of patients with BT, BB, and BL combined. Thus, patients with LL had significantly more hypogonadism as evidenced by elevated LH and FSH ($p < 0{\cdot}001$). Mean testosterone levels were not different between any of the four groups although there were more low values in patients with LL.

In the entire study population, both BI and anti-PGL-I IgM increased from the tuberculoid to the lepromatous pole of the disease spectrum. Patients with LL had significantly higher BI than those with BT ($p < 0{\cdot}01$) and significantly higher anti-PGL-I IgM than patients with BB and BT

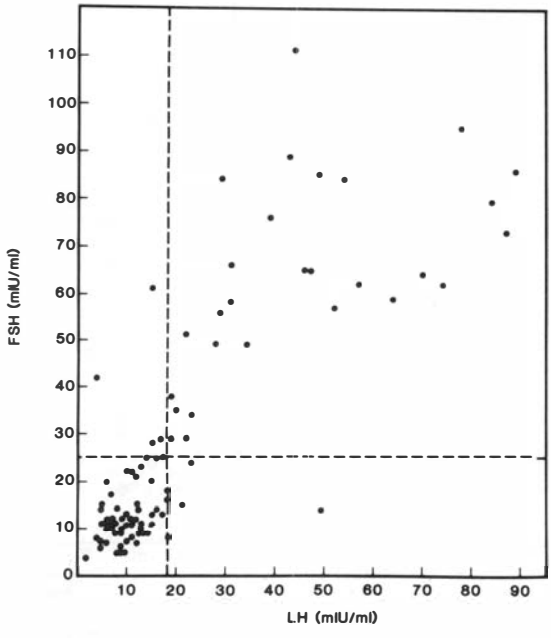

Figure 2. Luteinizing hormone (LH) *vs* follicle-stimulating hormone (FSH) for all leprosy patients ($r = 0{\cdot}82$ $p < 0{\cdot}001$).

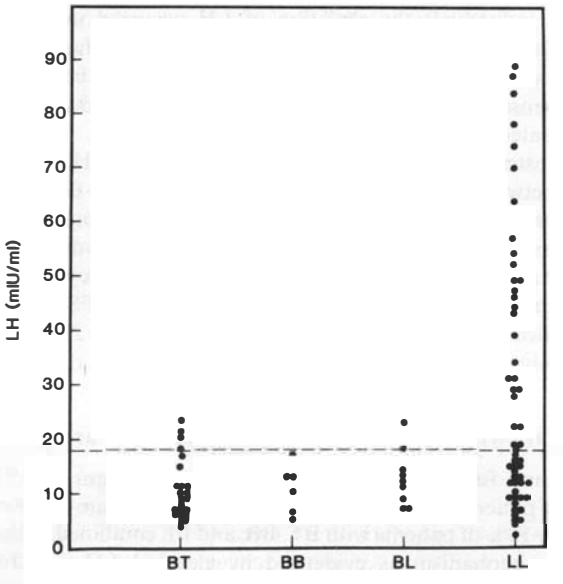

Figure 3. Luteinizing hormone (LH) by Ridley–Jopling disease classification. LL significantly higher than BL, BB, BT ($p < 0{\cdot}001$) by Bonferroni test. Dotted line is cut-off for normal range of LH (18 mIU/ml).

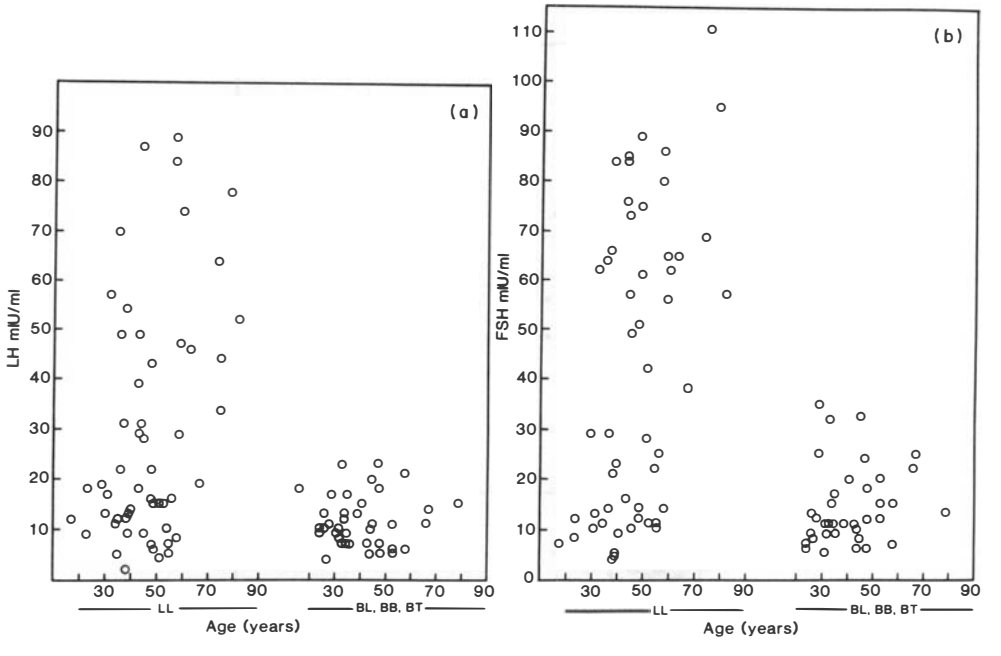

Figure 4(a). Luteinizing hormone (LH) *vs* age for LL patients and BL, BB, BT combined (for LL $r = 0{\cdot}37$, $p < 0{\cdot}01$; for BL, BB, BT $r = 0{\cdot}07$, $p > 0{\cdot}05$). (b) Follicle-stimulating hormone (FSH) *vs* age for LL patients and BL, BB, BT combined (for LL $r = 0{\cdot}46$, $p < 0{\cdot}001$; for BL, BB, BT $r = 0{\cdot}19$, $p > 0{\cdot}05$).

($p < 0{\cdot}01$ for LL *vs* BB; $p < 0{\cdot}001$ for LL BT, data not shown). As observed in previous studies,[5,6] anti-PGL-I IgM correlated with BI significantly for the entire study population ($r = 0{\cdot}50$, $p < 0{\cdot}001$) and more strongly in the case of the recently diagnosed individuals ($r = 0{\cdot}986$, $p < 0{\cdot}001$).

There was no statistically significant relationship between BI and FSH, LH, or testosterone, or between antiPGL-I IgM and any of these hormones regardless of whether all patients were analysed or just the recently diagnosed individuals.

A significant correlation was seen between age and levels of LH and FSH in LL patients but not in BL, BB and BT combined (Figure 4(a) and (b)). A statistically significant correlation was seen between duration of disease and both FSH (Figure 5) and LH ($r = 0{\cdot}30$, $p < {\cdot}05$ data not shown). However, when age was taken into account by partial correlation analysis only FSH was significantly correlated with duration of disease.

Discussion

A random survey of adult males in the New York Regional Hansen's Disease programme indicates that primary hypogonadism and testicular failure is a consequence of leprosy in a significant number of lepromatous patients. Roughly half of the lepromatous patients surveyed were affected as evidenced by elevated LH and FSH serum levels (> 18 and 25 mIU respectively) as well as reduced testosterone levels (< 300 ng/dl) in one quarter of LL patients. This is in agreement with previous studies that have shown changes in LH, FSH and/or testosterone in lepromatous males.[8–11] Half of the individuals with elevated LH had normal testosterone levels, indicating that damage to Leydig cells was not so extensive as to prevent compensation by elevated LH levels. These results

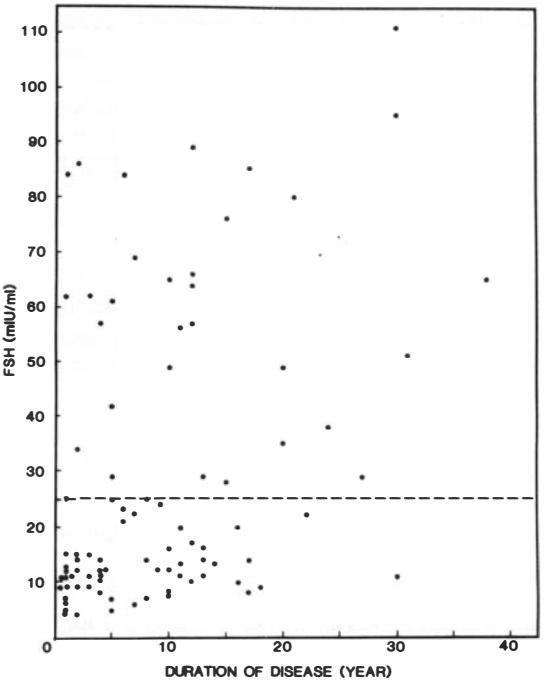

Figure 5. Follicle-stimulating hormone (FSH) *vs* duration of disease. Correlation between FSH and duration of disease; $r = 0{\cdot}37$, $p < 0{\cdot}02$, when age is taken into account by partial correlation analysis.

indicate that LL patients should be routinely screened for hypogonadism. Elevated FSH and/or LH detected hypogonadism in about half of the patients screened, while decreased testosterone was evident in only a quarter of the patients. Therefore, it is recommended that all three hormone levels be determined. Routine screening of BL and paucibacillary patients may not be cost-effective. However, should they be symptomatic, i.e. complain of impotence, they should be tested for hypogonadism. Toward this end, questions on sexual function and impotence should be a routine part of the examination.

Hypogonadal patients complaining of impotence were offered testosterone replacement therapy with 200 mg testosterone enanthate (delatestryl, Squibb, Princeton, NJ) twice monthly. Most of these patients expressed satisfaction with the replacement therapy. Further urologic and/or psychiatric evaluation was indicated in a minority of cases. Future studies on the frequency and quality of intercourse in those patients will aid in evaluating the success of replacement therapy.

The strong correlation seen between LH and FSH ($r=0{\cdot}82$, $p<0{\cdot}001$ for the entire study population; $r=0{\cdot}95$, $p<0{\cdot}001$ for the newly diagnosed group) was somewhat unexpected. Elevations in LH may be underdiagnosed to a greater extent than elevations in FSH when single samples are used as a result of the pulsatile secretion of LH.[12]

A study of disease activity parameters showed that the BI obtained in skin biopsy correlated well with the level of antiPGL-I IgM, in keeping with previous studies.[5,6] However, neither the BI nor antiPGL-I IgM showed any statistically significant relationship to FSH, LH nor testosterone in either the entire patient study group or the recently diagnosed group.

In males without leprosy FSH and LH have been reported to increase with ageing,[13] however, the correlation between duration of disease and FSH herein reported was independent of age. This is in apparent agreement with the findings of Ree *et al.*[10] and would indicate that infertility may precede hypogonadism. Many factors may contribute to testicular dysfunction, including the degree of testicular involvement and frequency and intensity of orchitis resulting from erythema nodosum leprosum (ENL), the immune-complex disorder of lepromatous leprosy. Other immune mechanisms could also play a role in both the hypogonadism and infertility of lepromatous orchopathy. Wall *et al.*[14] found increased cell-mediated immune response to testis extract in 9 of 13 LL males with evidence of testicular dysfunction compared to tuberculoid and normal subjects. This study suggests that testicular damage as a result of lepromatous leprosy is irreversible. However, longitudinal studies will be required to corroborate these findings and interpretations.

Acknowledgments

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