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Hormonal changes in human leprosy

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Summary In an attempt to define the extent of disturbances of testicular–pituitary function in leprosy, a study has been carried out on an unselected group of male patients attending a leprosy treatment centre, who were not obviously suffering from testicular atrophy or gynaecomastia.

Introduction

Involvement of the testis in male patients with leprosy is well documented and may be associated with impotence, sterility and gynaecomastia.[1] Testicular histology shows atrophy of seminiferous tubules, with hypertrophy and clumping of Leydig cells and hyalinization of the small and medium sized vessels.[2] The hormonal functions of the testes have been studied by a number of workers, usually in patients with testicular atrophy and gynaecomastia.[3–5] In these particular patients, androgens are generally diminished and gonadotrophins increased. The pathogenesis of the testicular damage is uncertain, though Wall and Wright[6] found that testicular germinal cell antibodies were present in 75% of lepromatous patients, and postulated that autoimmunity, Erythema–Nodosum–Leprosum immune complex damage and direct invasion by *Mycobacterium leprae* may all be contributory.

It is generally accepted that a classical feedback system operates between the testis and the pituitary gland.[7] The interrelationship between androgen and luteinizing hormone (LH) levels appears to be reasonably straightforward but may operate following conversion of testosterone to oestrogen. The testicular factor which controls follicle-stimulating hormone (FSH) levels is probably a poorly characterized non-oestrogenic, non-adrogenic substance known as

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inhibin. Some synergism between these two gonadotrophins in both Leydig cell function and spermatogenesis may occur,[8] but in general plasma levels of LH reflect the function of interstitial cells, and of FSH the seminiferous tubules.

Patients and methods

The patients were randomly selected males attending the Port Moresby Treatment Centre. Prepubertal boys and patients with obvious gynaecomastia were excluded from the study, but otherwise no specific clinical examination for testicular function was made. In Port Moresby, but not as a rule elsewhere in Papua New Guinea, leprosy patients are classified on the 5-point scale of Ridley and Jopling.[9] For the purpose of this study, the patients were classified into 2 groups only, lepromatous (Ridley and Jopling LL and BL) or tuberculoid (BT and TT). Patients with pure borderline (BB) or indeterminate (I) leprosy were also excluded from the study.

Venous blood was taken from the patients into heparinized tubes between the hours of 9.00 and 10.30 a.m.: plasma was immediately separated, and stored at − 20°C until being flown to Australia, packed in dry ice, for LH, FSH and testosterone estimations.

FHS and LH were assayed by a double-antibody radio-immunoassay using LER-907 obtained from the National Pituitary Agency, USA as standard for both FSH and LH and antisera supplied from the same agency. I^{125}-labelled FSH was obtained from Sorin Nuclear, Brussels, and commercially obtained goat anti-rabbit gamma globulin used for precipitation.The normal male range for both FSH and LH is 2–10 m IU/ml.

Testosterone was measured by radio-immunoassay using pure standard and tritium-labelled testosterone obtained from the Radiochemical Centre, Amersham, UK, and New England Testosterone rabbit anti-serum NEA-042A. Samples were extracted with ether before assay, and incubated at 4° C overnight. The normal male range is 10–35 nmol/l.

The significance of differences between means was estimated by Student's 't' test. The correlation coefficient, r, was computed automatically on an HP32E calculator: the significance of r was calculated from the equation:

$$t = r\sqrt{\frac{n-2}{1-r^2}}$$

Results

There were 97 patients in the study: their ages and type of leprosy are listed in Table 1. The mean age of the lepromatous patients (L) (33.7 ± 10.8 years) was significantly higher than that of the tuberculoid (T) patients (28.4 ± 10.1 years,

Table 1

	Age distribution of the patients	
	Lepromatous	Tuberculoid
15–19	4	6
20–29	25	9
30–39	21	11
40–49	9	3
50+	7	2
Total	66	31

$t = 2.32$, $p < 0.05$): and the *L* patients had been on treatment significantly longer (9.34 ± 7.3 years) than the *T* patients (5.94 ± 5.7 years, $t = 2.473$, $p < 0.02$).

In the *L* patients, 36 (54.5%) had significantly elevated FSH levels (greater than 12 m IU/ml), compared with 3 (9.7%) of the *T* group. Using a χ^2 test with Yate's correction, this gave a value of 15.8457: for two degrees of freedom, a *p* value of less than 0.001. Likewise 13 (19.7%) of the *L* patients had elevated LH, against none of the *T* patients. The mean FSH and LH levels in the *L* patients were significantly higher than in the *T* patients (Table 2 and Figure 1).

Table 2

Group	No.	Mean FSH (mIU/ml)	Mean LH (mIU/ml)	Mean testosterone (nmol/l)
Lepromatous	66	17.75 ± 12.9* (3.6 — 5.4)†	7.52 ± 7.6 (0.8 — 54.6)	13.7 ± 10.01 (0.5 — 50.3)
Tuberculoid	31	7.91 ± 3.99 (2.0 — 23.8)	3.69 ± 1.25 (1.2 — 7.2)	19.5 ± 6.4 (9.3 — 37.1)

*± 1 Standard deviation.

†Range.

Difference between lepromatous and tuberculoid patients: FHS $t = 6.006$, $p < 0.001$; LH $t = 3.95$, $p < 0.001$; testosterone $t = 3.402$, $p < 0.001$.

Table 3. Effect of duration of treatment on FSH and LH levels in *L* patients

Duration of treatment (years)	No.	Percentage with elevated levels of FSH	LH
0–4	24	11 (46%)	2 (8.3%)
5–9	16	8 (50%)	4 (25%)
10–14	11	6 (54%)	2 (18%)
15+	15	11 (73%)	(5) (33%)
Total	66	36 (54.5%)	13 (19.7%)

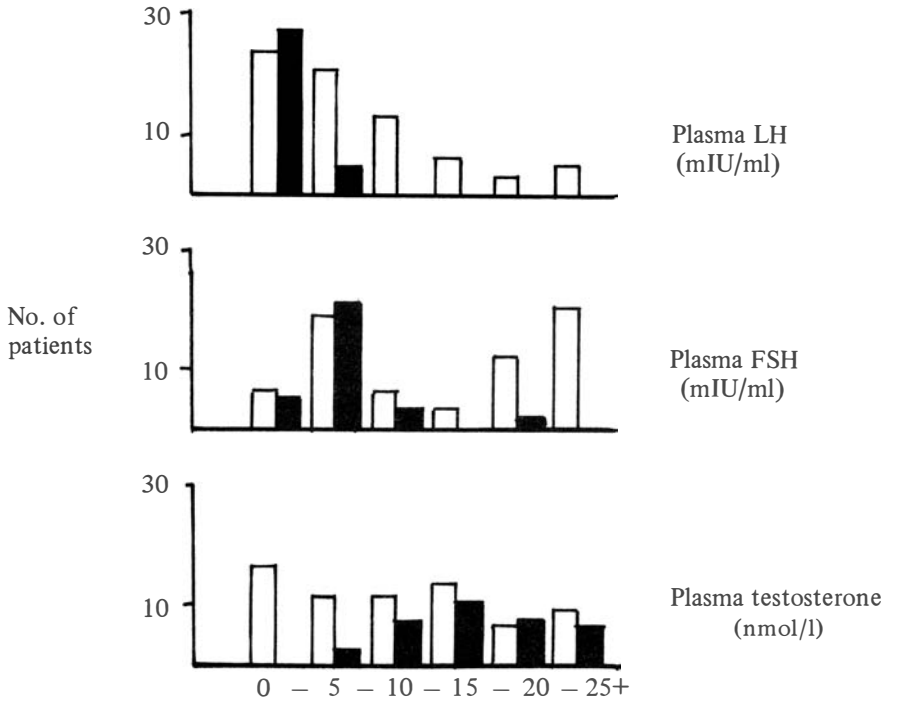

Figure 1. Distribution of Serum FSH, LH and testosterone in male *L* and *T* patients. □, *L* patients; ■, *T* patients.

Among the *L* patients, there was a significant relation between FHS ($r = 0.3199$, $p < 0.02$) and LH ($r = 0.4755$, $p = < 0.01$) with duration of treatment (Table 3).

No positive correlations between gonadotrophin levels and either duration of treatment or age were found in the *T* patients, suggesting that the changes in the *L* patients are not due to increasing age.

Plasma testosterone levels were significantly lower in the *L* patients (Table 2) but there was no correlation with either age or duration of treatment. A significant negative correlation was found between testosterone and both LH ($r = -0.3655$, $t = 3.14$, $p < 0.01$) and FSH ($r = -0.3248$, $t = 2.7474$, $p = < 0.01$) in the *L* patients.

Discussion

The early impact of lepromatous leprosy on the testis, as with many other toxic agents such as heat, irradiation and mumps, is on the seminiferous tubules rather than the interstitial cells of Leydig. This is reflected in elevation of FSH being at a much earlier stage than LH: infertility rather than hypogonadism is

the clinical result of this, though hypogonadism with or without gynaecomastia may occur later. There are few studies of the fertility of lepromatous patients: Kumar *et al.*[10] reported a significantly lower fertility and birth rate among the spouses of lepromatous males in India than in a control group of non-leprous patients. A study of fertility of male leprosy patients is now under way in Papua New Guinea. Morley *et al.*[5] found a significant positive correlation between duration of disease and basal LH, but do not comment on the relationship with FSH: their study population was, however, significantly different, with respect to the age of their patients (14 ± 16.1 years), from the present study, and a direct comparison is therefore not possible.

The normal levels of gonadotrophins in the *T* patients is strong confirmatory evidence that testicular damage does not occur in this group of patients. Job and Macaden[11] described 3 patients with tuberculoid granulomata of the testes during reactional phases: the diffuse damage that occurs in lepromatous leprosy was not seen. Thus clinicians involved in the care of leprosy patients can in practice safely ignore testicular function in tuberculoid (TT and BT) patients.

All the patients, in both the *L* and *T* groups, were being treated with standard doses of Dapsone at the time of the study. The standard regime in use in Papua New Guinea for all forms of leprosy has been Dapsone 200 mg twice a week: this was changed to Dapsone 100 mg daily about 1 year before the study was undertaken. In non-leprous patients Dapsone has not been reported to lead to testicular damage, and the normal levels of FSH and LH in the *T* patients suggest that this treatment was not the cause of the abnormalities. Of greater significance is the apparent failure of treatment to prevent testicular damage. If part at least of the damage is due to immune complex vasculitis, anti-mycobacterial treatment could aggravate the problem.

Throughout the world, including Papua New Guinea, registered leprosy is commoner in males than in females, and lepromatous leprosy is generally agreed to be commoner in males after puberty than before. These facts may reflect a hormonal dependence of *Mycobacterium leprae*, or alternatively may result from a steroid-modulation of immune processes. If so testicular failure may have a beneficial effect on the course of the disease, and replacement hormonal therapy may be harmful. However, so far there is no firm evidence to support this hypothesis, and in its absence it would seem unfair not to use testosterone therapy. As far as we are aware, there have been no combined histological and hormonal studies of patients with lepromatous leprosy. Dass *et al.*[4] measured plasma testosterone in lepromatous patients, in some of whom testicular biopsies were performed but no correlation between the two was attempted. If testicular damage occurs at an early stage of the disease biopsies from a large number of lepromatous males at various stages of their disease would need to be obtained to study the natural history of progression.

The history of onset of leprosy in Papua New Guinea is frequently chronologically imprecise, and in this paper duration of treatment refers to the time

lapse since the patient first presented with clinical symtoms, taking no account of the regularity of treatment. Approximately one-half of the *L* patients seen within 3 years of starting treatment had significantly elevated FSH levels: and if the regression line of FSH against duration of treatment is extrapolated backwards, it crosses the upper limit of normal 4 years before treatment is started. It would thus seem that in many patients testicular damage has been gradually occurring for several years before the actual presentation for treatment.

In much of the world, the stigma of leprosy is a considerable social burden. Sterility and impotence will aggravate an already disastrous situation, particularly since many patients, and probably even more physicians, are incapable of rational discussion of human sexuality. A greater emphasis on this aspect of leprosy is urgently required to properly treat the disease in all its aspects.

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