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Hormone Profile in Lepromatous Leprosy. A Preliminary Study[1]

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The testicular atrophy, gynecomastia, and symptoms of sexual dysfunction often seen in patients with Hansen's disease have long since made leprologists regard the endocrine system with suspicion ([1, 6, 10, 12, 15, 16, 19]). Yumnan, *et al.* observed, in addition, that leprosy and myxedema had several clinical features in common but found thyroid function in leprosy to be within normal limits. Martin, *et al.* ([16]) noted that plasma testosterone fell in leprosy patients with gynecomastia and that the urinary excretion of gonadotrophins rose progressively from normal in patients without gynecomastia to hypogonadal levels in patients with gynecomastia. They suggested that leprosy is an "acquired Klinefelter's syndrome." Morley, *et al.*, ([19]) reported raised mean basal serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in patients with lepromatous leprosy, a significant rise in both gonadotrophins in response to luteinizing hormone releasing hormone (LHRH), and a significant positive relationship between basal LH and the duration of leprosy.

Some investigators believe that gynecomastia and other feminine characteristics are produced by an imbalance between estrogen and testosterone ([6, 10]). Liver dysfunction has been implicated as a cause of the rise in circulating estrogen in relation to an already lowered serum testosterone ([6, 10]).

Variations in serum and urine hormones in leprosy, though reported, have thrown little light on the cause-effect relationship of the biochemical to the clinical findings. It is evident that the hormonal changes accompanying leprosy have been poorly documented. We report here the results of a preliminary investigation of the hormonal status in Hansen's disease.

MATERIALS AND METHODS

Eleven male patients with lepromatous leprosy from the Schieffelin Leprosy Research and Training Centre (S.L.R.&T. Centre), Karigiri, were studied. Since the study was of a preliminary nature, the patients chosen were representative of the patient population in the S.L.R.&T. Centre but deliberately included those with clinical features suggestive of endocrinopathy. They therefore represented disease of varying duration and activity as well as reactive states. Their ages ranged from 27 to 39 years (mean 33 years). The duration of disease varied from 3 to 26 years (mean 16 years), and nine were on regular treatment. Six of the patients were married, and three were fertile. Secondary sex characters were fully developed in seven, three were impotent, six had orchitis, and four had gynecomastia. Ten of them gave a history of having had erythema nodosum leprosum (ENL), but only five of them were in reaction at the time of testing. Skin smears from four of the 11 patients were negative for AFB.

Serum triiodothyronine (T_3) and thyroxine (T_4) were measured by the radioimmunoassay (RIA) methods of Eastman, *et al.* ([9]) and Chopra ([4]), respectively. The method of Woldering, *et al.* ([26]) was used to measure the T_3-resin-uptake (T_3RU), and the Free Thyroxine Index (FTI or FT_4I), calculated according to Clark and Horn ([5]). Serum cortisol was estimated by the competitive protein binding (CPB) assay of

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TABLE 1. *Range of values of serum hormones in 11 lepromatous leprosy patients compared to the normal range (Mean ± 2 S.D.).*

Hormone	Patient range	Normal range
Triidothyronine (T_3) (ng%)	74–183	80–190
Thyroxine (T_4) (μg%)	3.7–14.3	5–12
T_3-resin-uptake (T_3RU) (%)	75–114	75–110
Free Thyroxine Index (FT_4I)	4.5–12.1	5–11
Thyroid stimulating hormone (TSH) (μU/ml)	3–8.3	2–8
Cortisol (μg%)	6.9–13.8	5–20
Prolactin (ng/ml)	1.68–22	2.6–9.9
Luteinizing hormone (LH) (mIU/ml)	20.2–58.3	5–20
Follicle stimulating hormone (FSH) (mIU/ml)	2.8–52.0	5–20

Beardwell, *et al.* (2). Serum thyroid stimulating hormone (TSH), LH, FSH, and prolactin were measured by a double antibody RIA using kits supplied by Biodata (SPA) (Hypo Lab S.A., Switzerland).

RESULTS

The range of values obtained for all the serum hormones studied is shown in Table 1. The normal range for T_3, T_4, FTI, TSH, and cortisol represent the range in the local population, which is used as the reference range in our laboratory. The hormones LH, FSH, and prolactin were estimated using commercially available kits, all sera being estimated in the same assay to avoid inter-assay error. Ten normal controls were included in each kit to standardize the test. The control values fell within the normal range defined by the manufacturers, and the quality control serum supplied with the kit gave fairly accurate values for each kit.

Figures 1 and 2 visualize the individual values in relation to the normal range.

We found that the thyroid hormones T_3 and T_4, FTI, TSH, and cortisol were within normal limits while LH, FSH, and prolactin were raised. The values of these three hormones, LH, FSH, and prolactin, were studied in relation to impotence, orchitis, gynecomastia, and the development of secondary sex characters (Table 2). Although there was a trend for the individual values to differ in relation to these variables, the number of patients studied was too small to give statistically significant results.

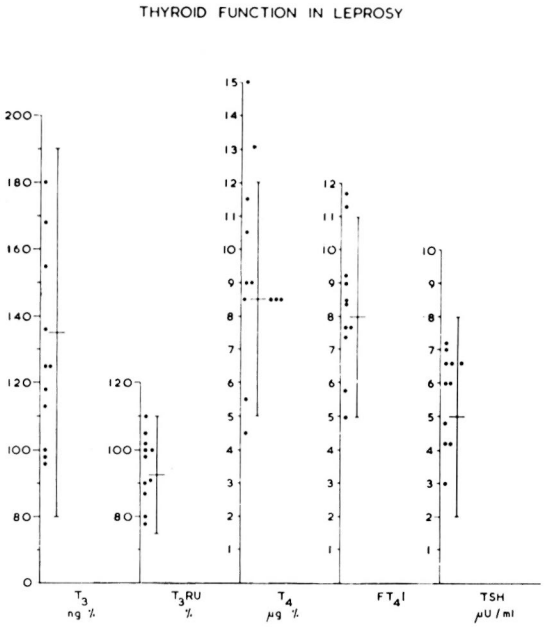

FIG. 1. Thyroid function in lepromatous leprosy showing the individual values against the normal range (Mean ± 2 S.D.).

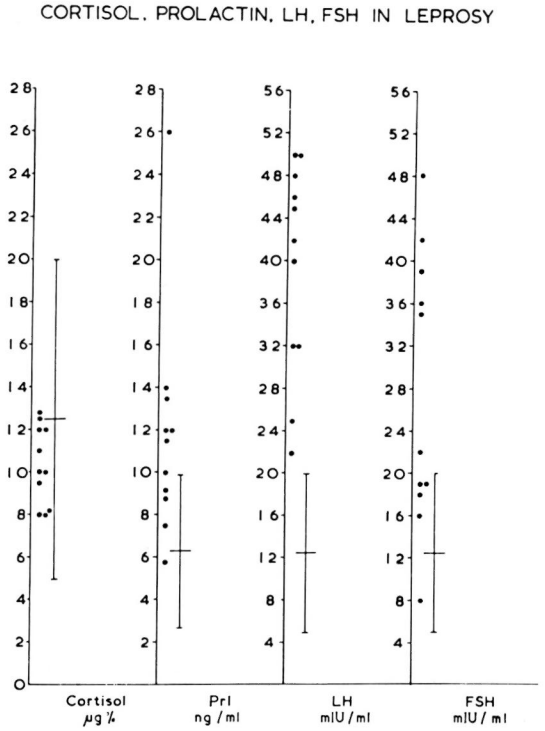

FIG. 2. Individual values for serum cortisol, prolactin (Prl), LH, and FSH compared to the normal range (Mean ± 2 S.D.). The latter three hormones are above the normal range while cortisol values are within normal limits.

TABLE 2. *Serum prolactin, LH, and FSH in relation to the presence of gynecomastia, orchitis, impotence, and secondary sex characters.*

	Number	Prolactin ng/ml Mean ± S.D.	LH mIU/ml Mean ± S.D.	FSH mIU/ml Mean ± S.D.
Total number of patients	11	11.8 ± 5.1	39.3 ± 9.5	27.5 ± 12.3
Gynecomastia				
Present	4	14.4 ± 7.3	43.0 ± 7.0	28.8 ± 10.3
No gynecomastia	7	10.4 ± 1.9	37.1 ± 10.1	26.7 ± 13.3
Orchitis				
Present	6	12.8 ± 6.4	43.5 ± 5.9	24.3 ± 8.1
No orchitis	5	10.8 ± 2.1	34.2 ± 10.5	31.2 ± 15.2
Secondary sex characters				
Not fully developed	4	11.3 ± 3.3	41.8 ± 11.6	35.5 ± 2.5
Fully developed	7	12.1 ± 5.8	36.4 ± 9.5	24.3 ± 13.7
Impotence				
Impotent	3	12.7 ± 0.9	45.6 ± 3.3	37.6 ± 3.1
Not impotent	8	11.5 ± 5.9	36.9 ± 9.9	23.6 ± 12.3

The values for prolactin were compared with those of ten normal controls, five males, and five non-pregnant females (Fig. 3). There was no significant difference between the males and females in the control group. The patient group, however, differed significantly from controls ($p < 0.01$).

All of the 11 patients had raised serum globulins. Blood sugar was normal in all cases.

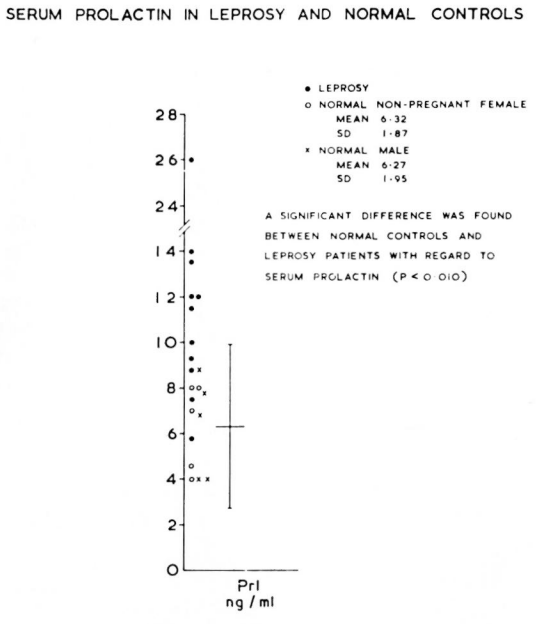

FIG. 3. Serum prolactin (Prl) levels in leprosy compared to normal controls (Student's *t* test).

DISCUSSION

The occurrence of testicular atrophy, sexual dysfunction, and gynecomastia in some male patients with lepromatous leprosy has long been recognized, but the endocrine basis of such changes remains to be determined.

It is known that testicular lesions follow direct invasion by the acid-fast bacilli ([12]). These lesions in the chronic stage closely resemble the histological features of Klinefelter's syndrome. In light of this finding, Martin, *et al.* ([16]) studied the pattern of excretion of urinary gonadotrophins and the levels of plasma testosterone in patients with lepromatous leprosy and gynecomastia and postulated that leprosy with leprous orchitis represents a form of acquired Klinefelter's syndrome. Morley, *et al.* ([19]), using more sensitive techniques of hormone assay, reported similar findings.

A universally acceptable hormonal basis for gynecomastia has not been established either in leprosy or in other disease states. The conventional hypothesis, first proposed by Glass, *et al.* ([11]), is that a damaged liver fails to inactivate endogenous estrogens. If this is true, raised gonadotrophin levels, as seen in our patients also, causing a further increase in circulating estrogens, would serve to worsen the clinical condition. A hyperestrogenic state thus induced would explain both the hypogonadism and also the feminization. In patients with liver

disease, however, the role of estrogens in producing gynecomastia remains in dispute. While some authors have reported elevated estradial levels, others have found these to be normal [3, 13]. There is some evidence indicating a hypothalamic defect [20]. It is tempting to speculate that one cause for hypothalamic dysfunction in these patients may be inhibition by excess circulating estrogen. Green, *et al.* [13] suggest that estrone or estriol may be of etiological importance in causing feminization in patients with chronic liver disease. Similar abnormalities of hypothalamic-pituitary-gonadal function have been described in patients with cirrhosis as well as in patients with normal liver function on chronic estrogen treatment [20, 25]. Serum prolactin also has been known to increase in response to circulating estrogen [25, 27]. Because of the infiltration of the liver in lepromatous leprosy as well as the reported abnormalities of liver function [8, 14, 17, 21, 22, 24], it is convenient to accept the theory that estrogens are in fact responsible for the gynecomastia seen in these patients [6, 10]. Morley, *et al.* [19], however, did not find any significant difference in serum levels of testosterone or 17β-estradiol in relation to gynecomastia and testicular atrophy in their lepromatous leprosy patients. It is more than likely then that there is another as yet undefined explanation for the feminization observed in leprosy.

The term "hormonal imbalance" as a cause of endocrinopathy in leprosy therefore retains much of its vagueness in spite of the introduction of specific radioimmunoassays for several hormones. We have found significantly raised circulating prolactin levels in our group of patients. To our knowledge, although gonadotrophins both in the serum and urine have been found to be elevated in leprosy, there is no report in the literature of the study of prolactin levels.

What role prolactin plays in producing the clinical picture of leprous endocrinopathy remains to be established. Turkington [23], using a prolactin bioassay, found no association between prolactin levels and gynecomastia of varying etiology. Morgan, *et al.* [18] found no relationship between serum prolactin measured by RIA and the gynecomastia of liver disease. To account for this they have postulated a discrepancy in biologically active prolactin and the immunologically active prolactin as measured in the assay. A study of a larger number of patients with lepromatous leprosy than those utilized in our study is required before we can understand in this disease the association, if any, between serum prolactin levels and gynecomastia and the significance of a raised serum prolactin.

Hypogonadism and sexual dysfunction have been shown to be associated with elevated prolactin levels. On the other hand, Grabstald and Swan [12] and El-Shiemy, *et al.* [10] found no relation between impotence and testicular involvement in their patients. They suggested a psychological cause for impotence. Prolactin levels were not determined. It is possible then that the sexual dysfunction in patients with lepromatous leprosy has something to do with raised prolactin levels independent of the histological lesions seen in the testes. Could lowering of the prolactin levels then restore sexual function despite testicular atrophy?

It is evident therefore from the results of our preliminary study of the hormonal profile in leprosy that a more detailed study of estrogens, androgens, gonadotrophins, and prolactin in relation to gynecomastia, testicular atrophy, and sexual dysfunction is warranted. A more valid explanation for these changes may be found by studying dynamic tests of endocrine function. Stimulation tests using the hypothalamic hormones, thyrotrophin releasing hormone (TRH), and LHRH would give an assessment of hormonal status and endocrine reserve and establish whether or not the feedback mechanisms and the hypothalamic-pituitary-end organ axis is intact.

SUMMARY

In a preliminary study, 11 male patients with lepromatous leprosy were evaluated with regard to endocrinopathy and hormonal status. Basal circulating hormone levels were estimated with a view to correlating the biochemical findings and clinical features. Thyroid hormones T_3 and T_4, Free Thyroxine Index (FTI), TSH, and cortisol were within normal limits, indicating that further study of these hormones would not be worthwhile. The finding of elevated

levels of prolactin as well as the gonadotrophins LH and FSH, however, promises to yield more valuable information if studied in greater detail in a larger group of patients.

RESUMEN

En un estudio preliminar, se evaluaron 11 pacientes del sexo masculino en relación a su estado endocrinopatológico y hormonal. Se midieron los niveles basales de algunas hormonas circulantes con la idea de correlacionar los hallazgos bioquímicos con las características clínicas de los pacientes. Las hormonas tiroideas T_3 y T_4, el índice de tiroxina libre (ITL), la hormona estimulante del tiroides (TSH), y el cortisol, estuvieron dentro de los límites normales por lo que no se insistió en el estudio de estas hormonas. Sin embargo, el hallazgo de que los niveles de prolactina y de las gonadotrofinas LH y FSH se encuentran elevadas resulta interesante y puede proporcionar información valiosa si el estudio se hace con más detalle en un número mayor de pacientes.

RÉSUMÉ

On a étudié, de façon préliminaire, l'état endocrinopathique et hormonal de 11 sujets de sexe masculin atteints de lèpre lépromateuse. Le taux de base de l'hormone circulante a été estimé dans le but de mettre en corrélation les observations biochimiques et les caractéristiques cliniques. Les taux des hormones citées ci-après se situaient dans les limites normales: les hormones thyroidiennes T_3 et T_4, l'Index Libre de Thyroxine, (FTI), la TSH, et le cortisol. Ceci indique dès lors qu'une étude ultérieure de ces hormones ne mérite pas d'être menée. L'évaluation observée du taux de prolactine, ainsi que l'élévation des taux de gonadotrophines LH et FSH, promettent cependant de fournir des informations plus valables, si ces hormones étaient étudiées dans plus de détails, et chez un nombre plus grand de malades.

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REFERENCES

1. Balakrishnan, S., Ramanujam, K. and Ramu, G. Adrenocortical function tests in lepra reaction. Indian J. Med. Res. **62** (1974) 1166–1170.
2. Beardwell, C. G., Burke, C. W. and Cope, C. L. Urinary free cortisol measured by competitive protein binding. J. Endocrinol. **42** (1968) 79–89.
3. Cameron, C. B. Urinary excretion of oestrone, oestradiol-17β and oestriol in patients with chronic liver damage. J. Endocrinol. **15** (1957) 199–205.
4. Chopra, I. J. A radioimmunoassay for measurement of thyroxine in unextracted serum. J. Clin. Endocrinol. Metab. **34** (1972) 938–947.
5. Clark, F. and Horn, D. B. Assessment of thyroid function by the combined use of the serum PBI and resin-uptake of ^{131}I-T_3. J. Clin. Endocrinol. Metab. **25** (1965) 39–45.
6. Dass, J., Murugesan, K., Laumas, K. R., Deo, M. G., Kandhari, K. C. and Bhutani, L. K. Androgenic status of lepromatous leprosy patients with gynecomastia. Int. J. Lepr. **44** (1976) 469–474.
7. Desikan, K. V. and Job, C. K. Review of postmortem findings in 37 cases of leprosy. Int. J. Lepr. **36** (1968) 32–44.
8. Dhople, A. M. and Balakrishnan, S. Liver function tests in leprosy. Indian J. Med. Res. **56** (1968) 1552–1558.
9. Eastman, C. J., Corcoran, J. M., Ekins, R. P., Williams, E. S. and Nabarro, J. D. N. The RIA of triiodothyronine and its clinical significance. J. Clin. Pathol. **28** (1975) 225–230.
10. El-Shiemy, S., El-Hefnawi, H., Abdel-Fattah, A., El-Okbi, M. and Farid, A. Testicular and epididymal involvement in leprosy patients with special reference to gynecomastia. Int. J. Dermatol. **15** (1976) 52–58.
11. Glass, S. J., Edmondson, H. A. and Soll, S. N. Sex hormone changes associated with liver disease. Endocrinology **27** (1940) 749–752.
12. Grabstald, H. and Swan, L. L. Genitourinary lesions in leprosy with special reference to problems of atrophy of testes. JAMA **149** (1952) 1287–1291.
13. Green, J. R. B., Mowat, N. A. G., Fisher, R. A. and Anderson, D. C. Plasma estrogens in men with chronic liver disease. Gut **17** (1976) 426–430.
14. Karat, A. B. A., Job, C. K. and Rao, P. S. S. Liver in leprosy. Histological and biochemical findings. Br. Med. J. **1** (1971) 307–310.
15. Koshy, T. S. and Karat, A. B. A. Assessment of pituitary-adrenal function in lepromatous leprosy—a preliminary communication. Lepr. India **45** (1973) 12–16.
16. Martin, F. I. R., Maddocks, I., Brown, J. B. and Hudson, B. Leprous endocrinopathy. Lancet **2** (1968) 1320–1321.
17. Mohanty, H. C. and Murti, R. S. Serum transaminase in leprosy. Lepr. India **45** (1973) 163–166.
18. Morgan, M., Jakobovitz, A. W., Gore, M. B. R., Wills, M. R. and Sherlock, S. Serum prolactin in liver disease and its relationship to gynecomastia. Gut **19** (1978) 170–174.
19. Morley, J. E., Distiller, L. A., Sagel, J., Kok, S. H., Kay, G., Carr, P. and Katz, M. Hormonal changes associated with testicular atro-

phy and gynecomastia in patients with leprosy. Clin. Endocrinol. (Oxford) **6** (1977) 299–303.

20. MOWAT, N. A. G., EDWARDS, C. R. W., FISHER, R., MCNEILLY, A. S., GREEN, J. R. B. and DAWSON, A. M. Hypothalamic-pituitary-gonadal function in men with cirrhosis of the liver. Gut **17** (1976) 345–350.
21. MUKHERJEE, A. and GHOSH, S. A concomittant study of liver function and coagulation factor in leprosy. Lepr. India **45** (1973) 19–28.
22. SHIRDE, A. V. and JUNNARKAR, R. V. Serum transaminase activity in leprosy in relation to liver damage. Int. J. Lepr. **35** (1967) 366–374.
23. TURKINGTON, R. Serum prolactin in gynecomastia. J. Clin. Endocrinol. Metab. **34** (1972) 62–66.
24. VERGHESE, A. and JOB, C. K. Correlation of liver function with the pathology of the liver in leprosy. Int. J. Lepr. **33** (1965) 342–348.
25. WIEDEMANN ECKEHART, E., SCHWARTZ, E. and FRANTZ, A. G. Acute and chronic estrogen effects of serum somatomedin activity, growth hormone and prolactin in man. J. Clin. Endocrinol. Metab. **42** (1976) 942–952.
26. WOLDERING, M. G., BAKKER, A. and DORRENBOS, H. The uptake of I^{131}-T_3 by resin—an *in vitro* test of thyroid function. Acta Endocrinol. **37** (1961) 607.
27. YEN, S. S. C., EHARA, Y. and SILAR, T. M. Augmentation of prolactin secretion by estrogen in hypogonadal women. J. Clin. Invest. **53** (1974) 625–655.
28. YUMNAN, I. S., KAUR, S., KUMAR, B. and RASTOGI, G. K. Evaluation of thyroid functions in leprosy. Lepr. India **49** (1977) 485–491.