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Gonadal function in lepromatous leprosy*

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Summary Gonadal function has been studied in 14 male patients suffering from lepromatous leprosy. Eleven out of the patients showed reduction in testicular size. Eight had azoospermia and four oligospermia. Gynaecomastia was noted in 12 patients. In only 2 recently discovered cases was this absent.

Twelve of our patients had increased basal and peak FSH responses to LHRH. The LH response to LHRH was heterogeneous. Four patients had normal basal and peak levels; 4 had normal basal levels with an increased response to LHRH; 4 had elevated basal and peak responses and the remaining 2 had elevated basal levels with normal peak responses to LHRH.

Testosterone was normal in all patients while oestradiol 17β and oestrone levels were significantly elevated. There was no correlation between basal and peak gonadotrophins and testosterone, oestradiol 17β, oestrone or any of the clinical parameters.

Introduction

Testicular involvement in lepromatous leprosy is very common with atrophy of the testis being reported in up to 50% of patients.[1–3] In contrast, the ovary is almost never involved. The testicular lesions are associated with direct invasion by acid-fast bacilli and post-mortem studies have demonstrated that this occurs in 90% of male patients. Both seminiferous tubules and Leydig cells

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are involved and the later stages are characterized by fibrosis and no outline of the tubules can be detected.[1-2]

Gynaecomastia may be seen in lepromatous leprosy with an incidence ranging from 8.6% to 83%.[3-4] Usually gynaecomastia is associated with testicular atrophy and is seen both with and without concomitant generalized feminization.[4]

High levels of urinary gonadotrophins were reported by Grabstald and Swan.[1] Martin *et al.*[5] confirmed this and also found reduced plasma testosterone and urinary oestrogens in lepromatous patients with gynaecomastia and testicular atrophy. Increased basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels with an exaggerated gonadotrophin response to LH-releasing hormone (LHRH) has been described in lepromatous leprosy. In contrast, the response was normal in those with the tuberculoid form of the disease.[3]

In the present study, we have evaluated hypothalmic–pituitary–gonadal relationships in males with lepromatous leprosy and correlated this with the clinical presentation.

Materials and methods

PATIENTS

Fourteen unselected male patients with proven lepromatous leprosy under treatment with dapsone either alone or in combination with Thalidomide were studied. Clinical details are given in Table 1.

EXPERIMENTAL PROTOCOL

The test procedure was performed between 8.00 and 8.30 h after an overnight fast. A needle inserted into an antecubital vein was kept patent by slow administration of normal saline. Three blood samples were drawn during a 30-min equilibration period. All subjects then received 100 μg luteinizing hormone-releasing hormone (LHRH) by rapid i.v. injection. Blood samples were drawn at 10-min intervals following LHRH. Thyrotrophin-releasing hormone (200 μg) and the dopaminergic antagonist, Metoclopramide (10 mg) were given 30 and 60 min after LHRH. Full details of the prolactin, thyrotrophin and gonadotrophin responses will be published separately.[6] The results of the patients were compared to 28 healthy controls aged 20–40 years who received the same protocol. Informed consent for the test procedure was obtained from both patients and controls.

METHODS

Serum LH, FSH, testosterone (T), 17β-oestradiol (E_2) and oestrone (E_1) were determined by previously described methods.[7] LH and FSH levels were

Table 1. Clinical features of patients with lepromatous leprosy

Case No.	Age	Duration of disease	Grade of gynaecomastia	Testis size (cm)		Spermogram		Motility
				Left	Right	Volume (ml)	Count	
1	27	1	0	2 x 3	2.5 x 3		AZ	
2	38	1	0	2.5 x 2	2 x 3	2.5	14×10^6/ml	15%
3	48	1	1	1.5 x 2	1.2 x 2.5	2.8	52×10^6/ml	30%
4	29	9	2	2 x 3	2.5 x 2	2.0	30×10^6/ml	50%
5	35	14	3	1.5 x 1.5	0.5 x 1		AZ	
6	40	15	2	1.5 x 1.5	1.5 x 1.5		AZ	
7	36	15	3	0.5 x 1	0.5 x 1		AZ	
8	40	15	1	1.5 x 2	1.5 x 2		AZ	
9	37	15	2	1.0 x 1.5	1.5 x 1.5		–	
10	43	17	3	2.5 x 1.5	2 x 1.5		AZ	
11	33	18	2	2.5 x 2.5	2.5 x 2.0	1.5	4×10^6/ml	60%
12	35	20	3	2.5 x 2.5	2 x 2.5	2.0	11×10^6/ml	35%
13	56	27	3	1.0 x 1.5	1 x 1.5		AZ	
14	42	30	1	2 x 1.5	2 x 3		AZ	

AZ = azoospermia; 0 = patient without any enlargement of the breast.

expressed by reference to the second International Reference Preparation of human menopausal gonadotrophins. The actual standard used in the assay was the International Reference Preparation of pituitary FSH and LH (69/104), which was kindly provided by the Division of Biological Standards and Control, Hampstead, London, England. Antisera to LH (final dilution 1 : 200,000) and FSH (1 : 400,000), were kindly supplied by the National Pituitary Agency, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Md. ^{125}I-Labeled LH and FSH were purchased from Cea-Sorin. Intra- and interassay coefficients of variation were as follows: 5.8% and 19.1% (LH) and 4.3% and 6.9% (FSH). E_2, E_1, and T were determined after pooling equal volumes of the three basal samples.

Student's *t*-test was used to compare responses in patients and controls.

Results

CLINICAL FEATURES (TABLE 1)

The age of the patients ranged from 27 to 56 years, the mean being 41.5 years. The duration of the disease process varied from 1 to 30 years. Thirteen out of 14 patients were married, but only 6 had their own offspring. In almost all cases, the children were born during the first years of the disease; only in one case was a child born 14 years after the disease was diagnosed. Libido was reported normal in 12 out of 14 patients. Hair distribution was normal in all cases with the exception of loss of eyelashes and eyebrows – a consequence of the primary disease. No change in sex hair distribution was found.

Gynaecomastia was classified according to Hall[8] into 3 grades and was found in 12 out of 14 cases. The 2 cases without gynaecomastia had the disease for less than 1 year. There was, however, no correlation between the severity of the gynaecomastia and duration of the disease. Thus, in case no. 14, there was only slight gynaecomastia after 30 years of leprosy.

The testes were clearly reduced in size in 11 patients. This became more evident with the increase in duration of the disease. All patients with leprosy for 10 years or longer had small hard testes. Semen analysis was performed successfully in 13 patients. Eight patients showed azoospermia, while in 4, oligospermia was found with sperm counts ranging from 4×10^6/ml to 30×10^6/ml. Case 3 had a count of 52×10^6/ml. No correlation between duration of the disease and the spermogram could be demonstrated.

GONADOTROPHINS (TABLE 2)

Normal values for both LH as well as FSH have been defined as values within 2 s.d. of the mean in the controls. Using these criteria, 4 of the patients had normal basal and peak LH responses to LHRH. Another 4 had normal basal

Table 2. Laboratory findings

Case no.	LH (mIU/ml) Basal	LH (mIU/ml) Peak	FSH (mIU/ml) Basal	FSH (mIU/ml) Peak	Testosterone T(ng/ml)	17β oestradiol E_2 (pg/ml)
1	11.3	58.6	6.6	10.6	12.0	68
2	6.1	200	10.4	19.0	9.5	80
3	3.5	71.6	13.2	24.0	6.0	42
4	5.9	214.8	12.4	29.3	3.2	42
5	42.4	191.4	55.3	83.1	6.0	50
6	77.7	302.7	71.0	120.2	4.7	46
7	46.2	196.6	33.3	44.9	4.5	52
8	28.4	80.0	42.1	71.0	8.0	64
9	49.6	107.8	44.4	61.7	4.2	54
10	10.6	31.6	28.7	43.6	2.9	70
11	4.0	34.6	3.5	5.1	8.0	46
12	5.3	129.1	12.9	22.7	4.3	52
13	24.1	50.0	11.8	191.0	6.5	60
14	7.2	349.4	11.0	41.8	3.9	52
Mean	24.5	118.9	25.6	42.1	5.98	55.6
± s.d.	23.8	90.1	21.5	36.7	2.6	11.3
Controls						
Mean	11.5	57.1	5.9	9.4	5.9	22.1
± s.d.	4.2	13.9	2.1	2.7	2.0	6.9

levels with exaggerated LH responses to LHRH. A further 4 had elevated basal and peak LH responses and the remaining 2 subjects had high basal LH levels, but their response to LHRH was normal.

Twelve out of the 14 patients had high basal levels of FSH with an exaggerated peak response to LHRH. In general, the highest levels of FSH were observed in patients who had lepromatous leprosy longer than 14 years. There was, however, no significant correlation between the basal and peak gonadotrophins and duration of the disease, testicular atrophy, spermogram or gynaecomastia.

STEROIDS (TABLE 2)

As a group, the lepromatous patients demonstrated normal T levels, the mean ± s.d. being 5.9 ± 2.6 ng/ml as compared to 5.9 ± 2.0 ng/ml in the controls. All the patients showed an increase in E_2 levels. The mean in the patients was 55.6 ± 11.3 pg/ml as compared to 22.05 ± 6.9 pg/ml in the controls ($p < 0.01$). Similarly, the patients showed an increase in E_1 levels (92.5 ± 63.0 pg/ml) compared to 52.9 ± 15.5 pg/ml in the controls ($p < 0.001$). No correlation between T, E_2, E_1 or E_2/T and the various clinical parameters could be demonstrated. In addition, there was no correlation between steroid levels and the basal or peak level of gonadotrophins.

Discussion

Although it is well known that the testis is involved in leprosy, there is a paucity of data relating clinical findings with fertility potential and gonadotrophin secretion. In the present study, we found that 71% of our patients had reduction in testicular size. This is a high percentage compared to other studies which report testicular involvement in 10–50% of patients.[1,3] As the duration of the disease process progresses, more of our patients presented with testicular atrophy. Our patients had azoospermia or oligospermia. This however, did not correlate with the duration of the disease process. Azoospermia was observed in some patients with leprosy of 1 year's duration and oligospermia was noted in some after 18 years of the disease. The lack of association between sperm count and duration of disease is probably related to the pathogenesis of the testicular involvement in leprosy. In the initial phase, there is perivascular infiltration by lymphocytes and lepra cells.[1] Later, there is clumping of Leydig cells with tubular destruction. The final stage is characterized by fibrosis of the tubules. This progressive destruction explains the presence of low grade spermatogenesis.

Gynaecomastia was noted in 12 of our patients, only 2 recently discovered cases did not show this phenomenon. This percentage is much higher than that observed by Watson *et al.*,[4] and similar to the incidence reported by Morley *et al.*[3] Gynaecomastia was not related to the duration of the disease.

Twelve of our patients (85.7%) had increased basal and peak FSH responses to LHRH. This is compatible with previous observations.[9–10] In contrast to FSH, the LH response was heterogeneous. Four out of 14 had an LH secretory pattern similar to the controls. This is contrary to Morley *et al.*[3] who noted exaggerated LH as well as FSH responses. However, Dash *et al.*[10] found that the LH response to LHRH in lepromatous leprosy was not different from the controls. Four of our patients had normal basal LH levels with exaggerated responses to LHRH, indicating the presence of increased LH reserve. Two cases, in contrast, showed high basal LHs with a normal response to LHRH.

The normal LH profile in some patients indicates that Leydig cell function may be relatively spared. The high basal levels of FSH and the increased response to LHRH implies damage to the seminiferous tubule. Since all except 2 subjects had increased FSH levels, this is an indication that seminiferous tubule damage is common. This is supported by pathological studies showing invasion by acid-fast bacilli in 90% of cases.[2] Of interest was the high FSH level in 3 patients who had their own children. Conception evidently occurred prior to seminiferous tubule destruction. The one patient who had a child after 18 years of leprosy, had a normal LH and FSH profile. We could not demonstrate a correlation between duration of the disease and either of the gonadotrophins. Morley *et al.*[3] in contrast, did find a correlation with basal LH.

T was normal in all patients, while E_1 and E_2 were elevated. There was no relation to duration of the disease and no correlation with the gonadotrophins. This is contrary to what was found by Martin *et al.*[5] and Morley *et al.*[3] who noted lower T, E_2 and urinary oestrogens in lepromatous leprosy. Dash *et al.*,[9] in contrast, has observed elevated serum E_2. It is possible that the high plasma LH noted in some patients maintains normal T levels. The increased levels of E_2 and E_1 could result from direct testicular secretion, or aromatization from T and androstenedione respectively.[11–14] Alternatively the increased levels may be due to inadequate inactivation of oestrogens occasioned by deranged liver function.[15] Testicular secretion of E_1 accounts for less than 5% of E_1 production in normal man.[12] Thus nearly all the E_1 is accounted for by peripheral conversion of androstenedione and to a lesser extent E_2.[13] Similarly the testis only accounts for one-fourth of E_2 production in normal man.[11] It has been shown that the pathological testis secretes even less E_1 and E_2.[11–12] Hence it is most likely that the elevated E_1 and E_2 levels are due to increased aromatization rather than testicular secretion.

Finally, it should be stressed that all of the patients were receiving Dapsone and a few Thalidomide. It is not known as to whether these compounds contributed to the testicular pathology or the hormonal aberrations which we have observed.

In conclusion, it is apparent that most patients with lepromatous leprosy have increased FSH secretion; in contrast 78% had normal LH values. T was normal, although E_1 and E_2 were increased. We could demonstrate no correlation between gonadotrophins, steroids and the various clinical parameters.

References

1 Grabstald H, Swan LL. Genitourinary lesions in leprosy with special reference to atrophy of testes. *JAMA*, 1952, **149**, 1287.

2 Job CK. Gynaecomastia and leprous orchitis. *Int J Lepr*, 1961, **29**, 423.

3 Morley JE, Distiller LA, Segal J, Kob SH, Kay G, Katz M. Hormonal changes associated with testicular atrophy and gynaecomastia in patients with leprosy. *Clin Endoc*, 1977, **6**, 299.

4 Watson RA, Gangai MP, Skinsnes OK. Genitourinary Leprosy. *Urol Int*, 1974, **29**, 312.

5 Martin FIR, Maddocks I, Brown JB, Hudson B. Leprous endocrinopathy. *Lancet*, 1968, **2**, 1320.

6 Shilo S, Livshin Y, Sheskin J, Spitz IM. Gonadotrophin, prolactin and TSH secretion in lepromatous leprosy. (Submitted for publication.)

7 Spitz IM, LeRoith D, Livshin Y, Zylber-Haran E, Trestian S, Laufer N, Ron M, Palti Z, Schenker J. Exaggerated prolactin response to TRH and metoclopramide in primary testicular failure. *Fert Ster* (in press).

8 Hall PF. Gynaecomastia. In Astwood E (ed.), *Clinical Endocrinology*. New York: Grune & Stratton, 1960, Vol. I, p. 468.

9 Dash RJ, Samuel E, Kaur S, Rastogi D, Rastogi GK. Evaluation of male gonadal function in leprosy. *Horm Metab Res*, 1978, **10**, 362.

[10] Dash RJ, Kumar B, Sialy R, Rastogi GK. LH, FSH, responses to GnRH in lepromatous leprosy. *Horm Metab Res*, 1979, **11**, 413.

[11] Kelch RP, Jenner JR, Weinstein RL, Kaplan SL, Grumbach MM. Estradiol and testosterone secretion by human, simian, and canine testes in males with hypogonadism and in male pseudohermaphrodites with feminizing testes syndrome. *J Clin Invest*, 1972, **51**, 824.

[12] Weinstein RL, Kelch RP, Jenner JR, Kaplan SL, Grumbach MM. Secretion of unconjugated androgens and eostrogens by the normal and abnormal human testis before and after human chorionic gonadotrophin. *J Clin Invest*, 1974, **53**, 1.

[13] Wilson JD, Harrod JH, Goldstein L, Hemsell DL, MacDonald PC. Familial incomplete male pseudohermaphroditism. Type 1. *New Eng J Med*, 1974, **290**, 1097.

[14] Naftolin F, Ryan KF. The metabolism of androgen in central neuro-endocrine tissues. *J Ster Biochem*, 1975, **6**, 999.

[15] Dass, J, Murugesan K, Laumas KR, Deo MG, Kandhari KC, Bhutani LK. Androgenic status of lepromatous leprosy patients with gynaecomastia. *Int J Lepr*, 1976, **44**, 469.