Gonadotropin, Prolactin, and Thyrotropin Secretion in Lepromatous Leprosy

SHMUEL SHILO,* YOSEF LIVSHIN,† EDIT ZYLBER-HARAN,* JACOB SHESKIN,‡ AND IRVING M. SPITZ*

*From the *Department of Endocrinology and Metabolism, Shaare Zedek Medical Center, the †Department of Obstetrics and Gynecology, Bikkur Cholim Hospital, and the ‡Department of Dermatology, Hadassah University Hospital and Government Hospital for Hansen's Disease, Jerusalem, Israel*

Gonadotropin, PRL, and TSH secretion was determined in 14 patients (27 to 56 years of age) with lepromatous leprosy and in 28 controls. Each subject received LHRH (100 μg), TRH (200 μg), and the dopaminergic antagonist, metoclopramide (10 mg), at 30-minute intervals, with periodic blood sampling. On the basis of the LH response to LHRH, the patients were divided into two groups. Group I consisted of nine patients with an exaggerated LH response to LHRH. The remaining five patients of Group II had a normal response to LHRH. Mean basal and peak FSH responses to LHRH were increased in both groups, but were greater in Group I. Mean 17β-estradiol (E_2) levels were increased in both groups, whereas, testosterone values were normal. Basal PRL levels were similar to those in controls, but there was an increased PRL response to both TRH and metoclopramide in Group I patients. In contrast, Group II patients had PRL responses identical to controls. Both groups had increased TSH responses to TRH in the presence of normal basal thyroxine (T_4) and triiodothyronine (T_3) levels. The PRL response to TRH correlated with both basal and peak FSH responses to LHRH, but not with LH, E_2, nor testosterone. The TSH response did not correlate with either gonadotropins, E_2, or thyroid hormone levels. Similar abnormalities in PRL and TSH secretion have been described in patients with primary testicular failure.

Key words: gonadotropin, prolactin, thyrotropin, lepromatous leprosy.

It is well known that the testis is involved in lepromatous leprosy, and histologic studies have documented direct invasion by acid-fast bacilli (Grabstald and Swan, 1952; Morley and Melmed, 1979). Previous workers have demonstrated increased basal LH and FSH levels in patients with this condition, with exaggerated gonadotropin responses to LH-releasing hormone (LHRH) (Morley et al, 1977; Morley and Melmed, 1979).

We have previously demonstrated that patients with primary testicular failure, as well as those with azoospermia secondary to exposure to 1,2-dibromo-3-chloropropane (DBCP), have increased PRL responses to thyrotropin releasing hormone (TRH) and the dopaminergic antagonist, metoclopramide (MET) (LeRoith et al, 1981c; Spitz, et al, 1979b; Spitz et al, 1980; Spitz et al, 1981b). We have also shown that patients with primary testicular failure have exaggerated TSH responses to TRH in the presence of normal plasma levels of thyroid hormones (LeRoith et al, 1981b).

Thyroid function is reported to be normal in patients with lepromatous leprosy (Yumnam et al, 1977), although there have been no studies on the TSH response to TRH. In addition, there are no reports on PRL secretion in this condition. The aim of this study, therefore, was to evaluate PRL and TSH dynamics in patients with lepromatous leprosy. Our results have shown that those patients with the highest gonadotropin levels have exaggerated PRL responses to TRH and metoclop-

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Reprint requests: S. Shilo, M.D., Department of Endocrinology and Metabolism, Shaare Zedek Medical Center, Box 293, Jerusalem, Israel.

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ramide. There was also an increased TSH response to TRH in the presence of normal circulating levels of thyroid hormone.

Materials and Methods

Subjects

The patient population consisted of 14 men, 27 to 56 years of age, with lepromatous leprosy. The duration of the disease varied from 1 to 30 years and all were on treatment with dapsone, either alone or in combination with thalidomide. Nine of the subjects were azoospermic, and three were oligoazoospermic with sperm counts ranging from 4 to 30 million/ml. Full clinical details, including basal levels of testosterone, 17β-estradiol (E_2), estrone (E_1), LH, FSH, and peak gonadotropin responses to LHRH in these patients have already been published (Shilo et al, 1981). Twenty-eight healthy men, aged 21 to 41 years, served as controls.

Experimental Protocol

The test procedure was performed between 8:00 and 8:30 a.m., after an overnight fast. Administration of dapsone and thalidomide was stopped 24 hours prior to the test. None of the subjects were receiving any hormonal medication. A needle inserted into an antecubital vein was kept patent by slow administration of normal saline. Three blood samples were drawn during a 30-minute equilibration period. All subjects then received 100 μg LH, 200 μg TRH, and 10 mg MET, in sequence at 30-minute intervals. All agents were administered by rapid intravenous injection. Blood samples were drawn at 10-minute intervals following each agent and sampling continued for 60 minutes after the MET injection. We have previously shown in males that intravenous administration of 10 mg MET does not influence basal gonadotropin nor TSH levels, nor their response to releasing hormones (Spitz et al, 1979a). The control population received the same protocol. Informed consent for the test procedure was obtained from both patients and controls.

Methods

Serum LH, FSH, PRL, TSH, testosterone and E_2 levels were determined by previously described methods (LeRoith et al, 1981b; Spitz et al, 1977; Spitz et al, 1980). Values for LH and FSH are expressed with reference to the 2nd International Reference Preparation of Human Menopausal Gonadotropins (2nd IRP-HMG). Actual standard used in the assay was the 1st International Reference Preparation of Pituitary FSH and LH (69/104). This, as well as the PRL (75/504) and TSH standard (68/38), were kindly provided by the Division of Biological Standards and Control (Hampstead, London, England). Antisera to LH (final dilution 1:200,000), FSH (1:400,000), TSH (1:1,500,000) and PRL (1:400,000) were kindly supplied by the National Pituitary Agency, National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD, USA). Labeled (^{125}I) LH, FSH, PRL, and TSH were purchased from CEA-SORIN. Detailed competition curves showed that LH, FSH, TSH, and free alpha chain did not cross-react in the PRL assay. Competition of alpha chain was less than 1% in the assay for FSH and TSH and 10% in the assay for LH. In the LH assay, cross-reaction of TSH was 18% and that of FSH was 13%. In the TSH assay, cross-reaction was 10.6% for LH and 84% for FSH. In the FSH assay, competition for LH was 0.6% and for TSH was 3.7%. The marked cross-reaction of FSH in the TSH assay probably represents contamination of the FSH standard. Evidence for this is that euthyroid women with primary ovarian failure and high gonadotropin levels have normal basal TSH levels that are not increased by administration of LHRH (Hochner-Celnikier et al, 1982). Furthermore, hypothyroid patients with high TSH levels have normal gonadotropin levels and neither LH nor FSH concentrations are increased after TRH administration.

Total thyroxine (T_4), total triiodothyronine (T_3), and T_3 resin uptake (T_3RU), which is an indirect measure of thyroxine binding protein, were determined by using the commercial kits of Ames (Jerusalem, Israel). The free thyroxine index (FTI), which is the product of the T_4 and T_3 RU, was then calculated. This is analogous to and varies with the absolute concentration of free T_4 (Ingbar and Woeber, 1974).

Results

Gonadotropins and Steroids (Fig. 1)

On the basis of the peak LH response to LHRH, we have divided our patients into two groups. Group I was comprised of nine patients whose peak LH responses to LHRH ranged from 80 to 350 mIU/ml. Five patients in Group I had basal LH levels exceeding 28 mIU/ml; whereas in the remainder, basal LH levels were below 10 mIU/ml. Group II consisted of the remaining five patients, who had peak LH responses to LHRH ranging from 34.0 to 70.0 mIU/ml. All patients in Group II had mean basal LH levels below 11.0 mIU/ml, with one exception of 24 mIU/ml. Mean basal and peak LH responses to LHRH were greater in Group I than controls ($P < 0.001$). However, mean levels of LH in Group II were not different from controls (Fig. 1).

In Group I subjects, both basal and peak FSH levels were greater than in the controls ($P < 0.001$) or in Group II subjects ($P < 0.05$). Although FSH levels were markedly reduced in Group II, even in these patients basal and peak responses to LHRH were greater than in the controls ($P < 0.05$). In Group II, one patient (AZ) had a markedly elevated basal FSH level (21 mIU/ml) and peak FSH response to LHRH (54 mIU/ml) and was excluded from the mean of this group.

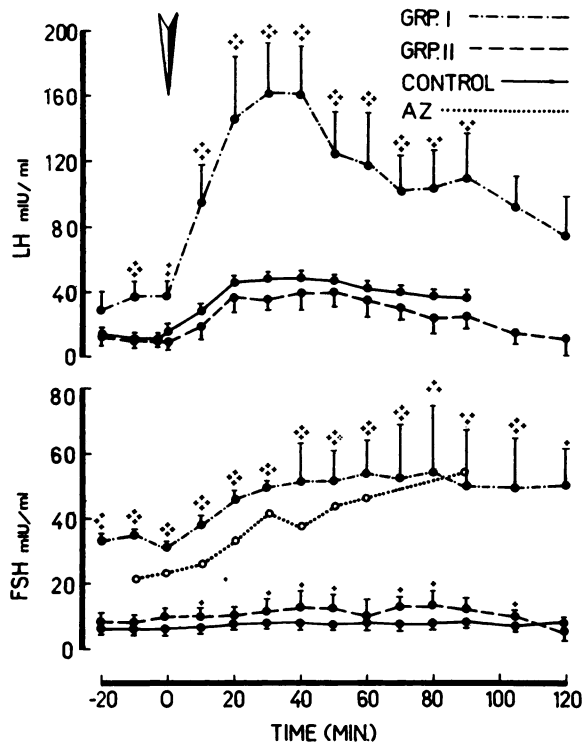

Fig. 1. LH (upper panel) and FSH (lower panel) response to 100 μg LHRH in Group I patients (– · – · – · –), Group II patients (– – – – –), and in controls (———). Values shown are mean ±1 SEM. Group II patient AZ (· · · · · ·) had markedly elevated FSH levels and has been excluded from the mean of this group. * = P values between patients and controls. $P < 0.05$; **$P < 0.01$; ***$P < 0.005$, and ****$P < 0.001$.

Mean E_2 levels were 55.1 ± 11.1 pg/ml in Group I and 57.2 ± 12.7 pg/ml in Group II. Both of these values were greater ($P < 0.001$) than those in the controls (22.1 ± 6.9 pg/ml). Mean testosterone levels were 5.9 ± 2.0 pg/ml in the controls, and were not significantly different in either Group I (5.3 ± 2.1 ng/ml) or Group II (7.1 ± 3.3 ng/ml).

PRL and TSH (Figs. 2, 3)

There were no differences in basal PRL and TSH levels before and after LHRH administration in either the controls or the patients. This indicates that endogenous gonadotropins do not cross-react in the PRL and TSH assays; neither did LHRH affect TSH or PRL levels in these subjects. Similar data has been reported previously (LeRoith et al, 1981b; Mortimer et al, 1973; Spitz et al, 1979a). Mean basal PRL levels were 9.6 ± 4.1 ng/ml in the controls and 8.5 ± 3.0 ng/ml and 7.5 ± 2.2 ng/ml in Groups I and II, respectively. These levels were not significantly different from one another. Distinct PRL peaks occurred following the administration of both TRH and MET. This is similar to what we have previously reported in primary testicular failure and DBCP-induced azoospermia (LeRoith et al, 1981c; Spitz et al, 1980). In both patient groups, as well as in the controls, the peak PRL response following TRH administration was evident at the 20-minute sample, and had decreased transiently at 30 minutes. Following injection of MET, another peak of PRL secretion was evident. This was maximum at the sample collected 20 or 30 minutes following MET administration. The PRL profiles to TRH and MET were similar in Group II patients and in the controls. However, Group I patients had significantly greater PRL responses to TRH and MET than had the controls.

Mean basal TSH levels were 1.9 ± 0.6 μU/ml in the controls and were not significantly different in Group I subjects (2.5 ± 0.9 μU/ml). In contrast, basal levels were increased ($P < 0.02$) in subjects of Group II (2.9 ± 0.6 μU/ml). The peak TSH response to TRH was 11.2 ± 4.8 μU/ml in the controls. There was an exaggerated response in both patient groups and peak levels were 17.6 ± 3.4 μU/ml in Group I ($P < 0.005$ compared with controls) and 17.1 ± 9.6 μU/ml in Group II ($P < 0.05$ compared with controls). Because both patient groups had similar TSH elevations following TRH, the results of the two groups have been combined in Fig. 3. There were no differences in mean T_4, T_3, and T_3 RU levels in the patients of both Groups I and II and the controls (Table 1). FTI levels were significantly greater in Group I than in Group II or the controls ($P < 0.005$). This level, however, was well within the normal range which extends from 4.1 to 13.5.

Correlations (Fig. 4)

The peak PRL responses to TRH correlated with both the basal ($r = 0.59$; $P < 0.05$) and peak ($r = 0.67$; $P < 0.01$) FSH responses to LHRH. There was, however, no correlation between the peak PRL response to TRH and basal E_2, testosterone, E_2:testosterone ratio, LH, or the peak LH response to LHRH. Neither basal nor peak TSH responses to TRH correlated with gonadotropins or E_2 levels. In addition, there was no correlation between PRL and TSH responses and serum T_4 and T_3 levels.

Discussion

Our patients with lepromatous leprosy had increased mean basal and peak FSH responses to LHRH administration. However, five of 14 had an LH secretory pattern similar to the controls. This is compatible with the observations of Dash et al (1979), but contrary to the findings of Morley et al (1977) who noted exaggerated LH, as well as FSH, responses. Elsewhere, we have shown that the gonadotropin pattern is unrelated to the duration of the disease process (Shilo et al, 1981).

Since all of our patients had increased FSH levels, we elected to group them according to the peak LH response to LHRH. On this basis, those patients with an increased LH response to LHRH (ie Group I) also had the highest FSH values and had exaggerated PRL responses to both TRH and MET. In contrast, PRL responses to TRH and MET were the same as responses of the controls in those patients who had intact LH responses to LHRH (Group II). Levels of FSH (with one exception) were significantly lower in Group II than in Group I subjects. Although the two groups had different PRL responses to TRH and MET, they both had normal basal PRL levels. This has been observed previously in testicular failure (LeRoith et al, 1981c; Spitz et al, 1979b; 1980; 1981b).

The peak response of TSH to TRH was greater in both groups of patients than in the controls. Basal levels, however, were increased only in Group II. This TSH pattern occurred in the presence of normal circulatory levels of T_4, T_3, and T_3 RU. We have described a similar TSH pattern in primary testicular failure (LeRoith et al, 1981b).

LHRH releases free alpha chain from the pituitary (Edmonds et al, 1975). There was however, no cross reaction of alpha chain in the TSH and PRL assays, and LHRH did not influence PRL or TSH secretion. These findings, together with the results of the cross-reaction studies detailed in the methods section, indicate that the increase in TSH and PRL levels consequent to stimulation with TRH represents a true increase in hormone levels.

It should be stressed that the high levels of gonadotropins are not in themselves responsible for the exaggerated PRL and TSH responses. Evidence for this is that male castrates with markedly elevated gonadotropin concentrations and low testosterone and E_2 levels, had PRL and TSH responses to TRH similar to controls (LeRoith et al, 1981a; 1981b). Furthermore, in the castrated rat,

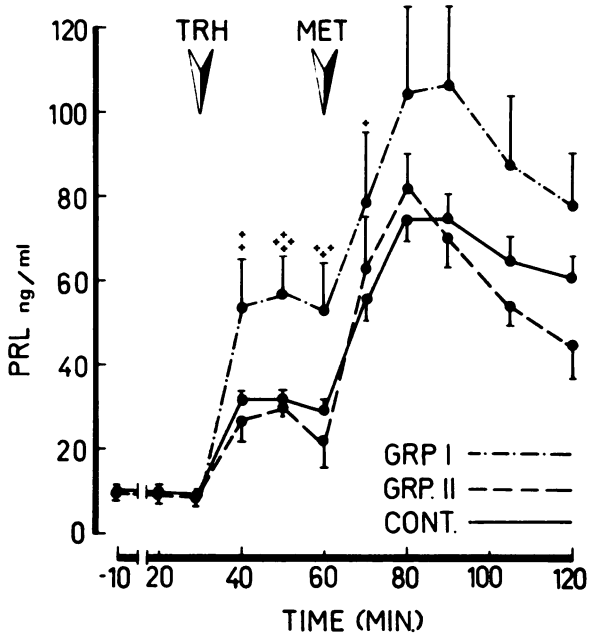

Fig. 2. PRL response to TRH and metoclopramide (MET) given at 30 and 60 minutes, respectively, in lepromatous patients of Group I and Group II and in the controls. See legend to Fig. 1 for details. *P values between patients and controls. *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$, and ****$P < 0.001$.

there is a decreased PRL response to both TRH and MET (Zylber et al, 1979). High gonadotropin levels are one marker of the severity of testicular involvement in leprosy. Hence, a greater PRL response occurs in patients whose testicular function is most severely compromised. A similar phenomenon has been shown to occur in primary testicular failure (Spitz et al, 1980). In contrast to the observations with PRL, the TSH response to TRH was increased in patients with both normal

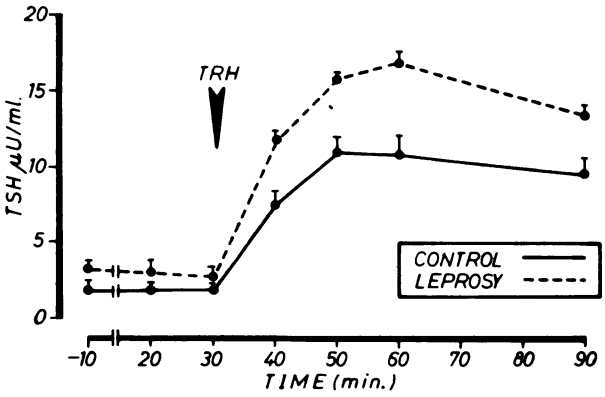

Fig. 3. TSH response to TRH given at 30 minutes in lepromatous leprosy patients (– – – –) and in controls (———).

TABLE 1. Levels of Total Thyroxine (T_4), Total Triiodothyronine (T_3), T_3 Resin Uptake (T_3RU), and Free Thyroxine Index (FTI) in Patients with Lepromatous Leprosy and in Controls*

	T_4 (μg/100 ml)	T_3 Total (ng/100 ml)	T_3RU (%)	FTI
Group I	8.2 ± 0.6 (9)†	135.4 ± 11.5	49.1 ± 1.9	7.9 ± 0.4‡
Group II	6.2 ± 0.6 (5)	114.8 ± 13.8	52.0 ± 3.2	6.3 ± 0.4
Controls	6.8 ± 0.1 (13)	137.0 ± 10.9	47.3 ± 0.5	6.4 ± 0.1

* Levels are mean ± SEM.
† Numbers in brackets refer to the number of subjects.
‡ $P < 0.005$ compared with controls.

and high levels of gonadotropins. Hence, the TSH profile would appear to be unrelated to the severity of the disease process.

Since estrogens are known to elevate PRL (Buckman and Peake, 1973; Carlson et al, 1974; Yen et al, 1974), it has been suggested that the exaggerated PRL responses to pharmacologic stimuli are an estrogen-induced phenomenon (LeRoith et al, 1981c; Spitz et al, 1979b; 1980; 1981b). This is supported by our observations that the increased PRL response to TRH in primary testicular failure is decreased following the administration of the estrogen antagonist, clomiphene citrate (Spitz et al, 1981a). However, among the patients in the present study, there was no direct correlation between the PRL response and E_2 concentration or E_2:testosterone ratio. Moreover, in our previously described patients with primary testicular failure and DBCP-induced azoospermia, there was no consistent relationship between the PRL response and estrogens (LeRoith et al, 1981c; Spitz et al, 1980). In addition, although estradiol levels were increased in DBCP-induced azoospermia, they were not uniformly elevated in primary testicular failure (LeRoith et al, 1981c; Spitz et al, 1980). In our lepromatous patients, E_2 levels were increased in both groups. This is contrary to some observations (Martin et al, 1968; Morley et al, 1977; Morley and Melmed, 1979), and in agreement with others who have reported elevated E_2 levels in this condition (Dash et al, 1978). The increase in E_2 might arise from direct testicular secretion, aromatization from testosterone, or inadequate peripheral inactivation (Shilo et al, 1981).

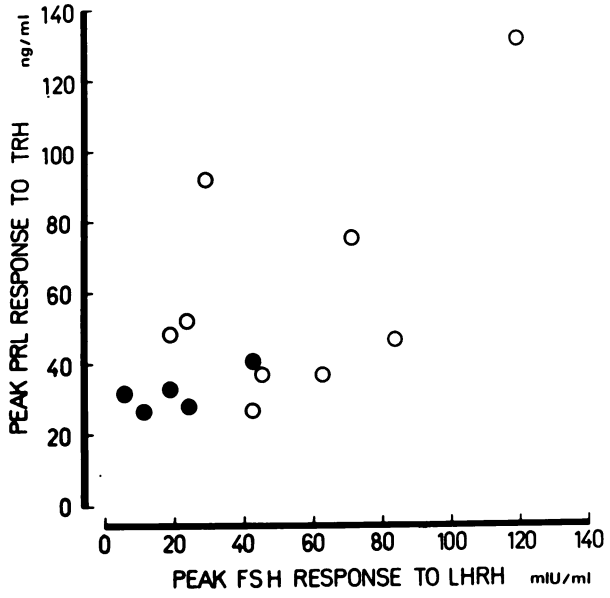

Fig. 4. Correlation between peak PRL response to TRH (ordinate) and peak FSH response to LHRH (abscissa) in Group I (○) and Group II (●) patients.

The exact mechanism for the exaggerated TSH response to TRH is also not clear. Whereas all agree that estrogens enhance PRL responsiveness to stimuli (Buckman and Peake, 1973; Carlson et al, 1974; Yen et al, 1974), there is controversy as to the effect of estrogens on TSH release (Smyth et al, 1977; Reymond and LeMarchand-Beraud, 1976). In both this and our previous studies, the TSH response to TRH did not correlate with E_2 levels (LeRoith et al, 1981b). Recent studies have shown that androgens modulate the TSH response to TRH (Morley et al, 1981).

It is possible that the exaggerated PRL and TSH responses may be related to other factors. Of interest in this regard was the correlation between the PRL response to TRH and basal and peak FSH levels. Such a correlation was not evident with LH. Several recent studies have shown that extensive tubular damage is associated with a selective increase in FSH levels. It has been suggested that inhibin, a nonsteroid, specifically regulates FSH secretion (Franchimont and Roulier, 1977). Our patients had increased FSH levels, whereas LH levels were normal in five of the 14 men. This is compatible with the histologic evidence of tubular destruction and fibrosis which occurs in patients with leprosy. The correlation between FSH and PRL levels suggests that inhibin might be in-

volved in the hyperresponsiveness of PRL. Our observations in DBCP-induced azoospermia, which predominantly involves the seminiferous tubules, supports this possibility (LeRoith et al, 1981c). Further studies are currently in progress to ascertain the relationship of inhibin to PRL secretion.

Finally, it should be stressed that all of our patients were taking dapsone and some, thalidomide. The administration of these agents was stopped 24 hours before the test procedure. Detailed analysis of the half-disappearance time of thalidomide in the human is not available. However, when repeated doses of dapsone are administered, traces of the compound are detectable for as long as 35 days after therapy has been discontinued (Weinstein, 1965). Furthermore, it is not known if these agents affect anterior pituitary hormone secretion.

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