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Increased thyrotrophin levels and loss of the nocturnal thyrotrophin surge in Sheehan's syndrome

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Summary

OBJECTIVE Since panhypopituitarism in patients with Sheehan's syndrome is due to massive pituitary necrosis with only minor hypothalamic involvement, we hypothesized that serum TSH levels would be low but its circadian rhythm preserved in these patients.

DESIGN AND PATIENTS Basal and TRH-stimulated mean afternoon (1500–1700 h) and nocturnal (0100–0300 h) TSH levels were determined in 10 patients with Sheehan's syndrome before and during T4/glucocorticoid replacement and in seven controls.

MEASUREMENTS Serum concentrations of T3, T4, free T4 (fT4) and cortisol were measured by radioimmunoassay; TSH, GH, PRL and LH were determined by immunofluorimetric assay.

RESULTS Afternoon TSH levels were markedly increased in Sheehan's syndrome patients compared with controls (3·3 ± 1·0 *vs* 0·5 ± 0·15 mU/l, respectively, $P = 0{\cdot}002$). At night, TSH levels remained unchanged in Sheehan's syndrome patients (3·3 ± 1·1 mU/l) but rose significantly in controls (1·1 ± 0·34 mU/l, $P = 0{\cdot}016$). The nocturnal TSH increment was significantly higher in controls than in patients (143 *vs* −4·9%, respectively, $P = 0{\cdot}0001$). In eight patients with normal serum fT4 levels during treatment, basal TSH levels decreased to 0·16 ± 0·05 mU/l ($P \leq 0{\cdot}008$), being barely detectable or undetectable in four patients. In the six patients with detectable TSH during treatment, nocturnal TSH increments were normal in four and blunted in two. There was a strong correlation between pre- and post-treatment basal TSH ($r = 0{\cdot}82$, $P = 0{\cdot}012$) and between pre- and post-treatment peak TSH after TRH ($r = 0{\cdot}91$, $P = 0{\cdot}0017$), but no significant correlation between TSH and thyroid hormone levels. The per cent ratio of peak TSH after TRH between treated patients and controls, an estimate of the relative size of the functional thyrotroph pool in Sheehan's syndrome patients, was 7%.

CONCLUSIONS Loss of TSH rhythm in Sheehan's syndrome is usually secondary to hormonal deficiency and results from maximally increased secretory activity of a decreased pool of thyrotrophs. The paradox of increased TSH levels and decreased thyroid function in Sheehan's syndrome could result from decreased TSH bioactivity and/or from a critically reduced thyrotroph population that fails to sustain sufficient TSH secretion in the face of rising serum thyroid hormone levels.

Thyrotrophin (TSH) is the major regulator of thyroid function. TSH secretion displays a distinctive circadian variation, with nadir levels in the afternoon and peak levels at night (Patel *et al.*, 1972; Weeke, 1973; Weeke & Gundersen, 1978; Brabant *et al.*, 1986, 1990; Greenspan *et al.*, 1986). This rhythm is thought to be predominantly determined by pulsatile secretion of TRH from the hypothalamus, but influences from extrahypothalamic sites as well as from other hormones are also involved (Fukuda & Greer, 1975; Morley, 1981; Brabant *et al*., 1991). Blunting of the nocturnal surge of TSH has been found in central hypothyroidism as well as in severe primary hypothyroidism, but not in mild primary hypothyroidism (Caron *et al*., 1986; Rose *et al*., 1990; Adriaanse *et al*., 1992a, b).

According to the dominant role of TSH in thyroid regulation, TSH levels in patients with central hypothyroidism should be decreased. However, basal TSH levels in this condition are either normal or slightly increased (Patel & Burger, 1973; Petersen *et al*., 1978; Faglia *et al*., 1979; Beck-Peccoz *et al*., 1985). This apparent discrepancy has been explained by studies showing decreased biological activity of circulating TSH in patients with central hypothyroidism (Petersen *et al*., 1978; Faglia *et al*., 1979; Beck-Peccoz *et al*., 1985). In addition, it has been suggested that the loss of the nocturnal surge of TSH could contribute to the development of thyroid hypofunction in these patients (Caron *et al*., 1986; Rose *et al*., 1990).

Since previous studies of TSH secretion in central hypothyroidism have included patients with hypothalamic and pituitary disease in which the relative contributions of the

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hypothalamic and pituitary deficiencies to the development of hypothyroidism are variable and often difficult to assess, we sought to investigate the rhythm of TSH secretion in a more homogeneous group of patients presenting with panhypopituitarism due to post-partum pituitary necrosis (Sheehan's syndrome). In this condition, the main pathological finding is massive destruction of the anterior pituitary gland with only minor or no involvement of the hypothalamus (Sheehan & Murdoch, 1939; Sheehan & Whitehead, 1963; Whitehead, 1963). Accordingly, Sheehan's syndrome can be regarded as a model of intrinsic pituitary deficiency syndrome where circulating TSH levels would be expected to be low but circadian rhythmicity preserved.

Subjects and methods

Patients and controls

Ten patients with Sheehan's syndrome (age range 26–61 (median 45) years) and seven age-comparable healthy control women (age range 23–49 (median 42) years) were studied. Informed consent was obtained from all participants after approval of the study protocol by the Hospital São Paulo-Escola Paulista de Medicina ethical committee.

The diagnosis of Sheehan's syndrome was suspected by clinical findings of panhypopituitarism and a positive history of massive post-partum uterine bleeding followed by amenorrhoea and failure of lactation. Despite the long time elapsed between the last delivery and the diagnosis (range 9 months–20 years, median 13 years), no patient had previously received hormonal treatment. The diagnosis was definitely established by computerized tomographic (CT) or magnetic resonance scans showing a normal sized empty sella in all patients, by low levels of circulating thyroid hormones, and by conventional dynamic testing of pituitary reserve showing blunted responses of GH and cortisol to insulin-induced hypoglycaemia (0·1 IU/kg body weight intravenously (i.v.)), of PRL and TSH to TRH (200 μg i.v.), and of LH to GnRH (100 μg i.v.). Hormonal evaluation of these patients is shown in Tables 1 and 2. Serum thyroid autoantibodies were negative in all but one patient (no. 7) who presented with elevated antimicrosomal antibodies (1 : 6400).

Study design

Patients were admitted to hospital 1 day before the study, when an indwelling i.v. catheter was placed in the forearm vein. The rhythm of TSH secretion was studied using a modification of the simplified approach described by Caron *et al.* (1986), with more frequent blood sampling and shorter collecting periods around the afternoon nadir and night peak times as described by Brabant *et al.* (1990) with blood sampling at 30 min intervals between 1500 and 1700 h and 0100 and 0300 h for TSH measurement. Meals were served at 0700, 1200 and 1730 h and consisted of approximately 2000 kcal/day. All patients remained in bed and were kept awake during the study. Sleep was allowed after the last night-time blood collection until 0900 h when fasting blood samples for TSH measurements were collected before and 15, 30 and 60 min after TRH (200 μg

Table 1 Thyroid evaluation in patients with Sheehan's syndrome

					TSH			
Patient	Age (years)	fT4 (pmol/l)	T4 (nmol/l)	T3 (nmol/l)	Basal (mU/l)	Peak (mU/l)*	AI (mU/l)	PI (%)
1	26	4·6	≤12·9	≤0·31	1·0	1·8	0·8	80
2	42	4·9	14·2	1·52	4·1	6·1	2·0	48
3	41	8·5	≤12·9	0·60	2·7	3·8	1·1	40
4	61	4·5	≤12·9	1·06	5·0	7·2	2·2	44
5	51	5·0	≤12·9	0·65	0·7	1·5	0·8	114
6	46	4·6	≤12·9	0·35	0·5	0·6	0·1	20
7	56	4·2	≤12·9	≤0·31	9·8	12·5	2·7	27
8	38	4·6	≤12·9	≤0·31	0·7	1·7	1·0	142
9	57	4·5	≤12·9	≤0·31	2·9	3·6	0·7	24
10	44	4·1	23·2	1·21	2·5	4·2	1·7	68
Mean ± SE	46·2 ± 3·3	5·0 ± 0·4	14·2 ± 1·0	0·7 ± 0·1	3·0 ± 0·9	4·3 ± 1·1	1·3 ± 0·3	61
Controls	36·4 ± 4·0	20·3 ± 1·7	94·0 ± 7·1	1·8 ± 0·2	0·7 ± 0·2	10·6 ± 3·0	9·8 ± 2·8	1435
Reference values		7·7–25·7	51–142	1·2–3·4	0·3–4·0		5·0–30·0	
P	NS	<0·01	<0·001	<0·01	<0·05	<0·05	<0·001	<0·001

* Maximal TSH levels after TRH administration.
AI, Absolute TSH increment after TRH (difference between peak and basal TSH levels); PI, per cent TSH increment after TRH [(AI/basal) × 100]. Values are expressed as mean ± SE. NS, Not significant.

Table 2 Individual basal and peak levels of GH and cortisol during insulin-induced hypoglycaemia, of PRL after TRH and of LH after GnRH in 10 patients with Sheehan's syndrome

	GH (μg/l)		Cortisol (nmol/l)		Prolactin (μg/l)		LH (IU/l)	
Patient	Basal	Peak	Basal	Peak	Basal	Peak	Basal	Peak
1	≤0·05	0·25	≤11·0	≤11·0	3·0	5·0	3·1	5·8
2	0·55	0·55	≤11·0	16·6	5·0	10·0	5·9	9·2
3	≤0·05	≤0·05	≤11·0	≤11·0	1·0	1·0	1·3	2·6
4	≤0·05	0·10	52·4	63·5	8·0	11·0	0·5	1·1
5	0·25	0·15	≤11·0	≤11·0	9·0	6·0	1·1	2·4
6	≤0·05	0·15	38·6	57·9	1·0	1.0	0·5	1·4
7	0·10	0·10	273·1	339·4	1·0	2·0	1·7	5·1
8	2·60	—	157·3	458·0	3·0	11·0	2·1	—
9	0·90	1·00	≤11·0	≤11·0	2·6	—	0·6	2·2
10	1·10	0·90	≤11·0	≤11·0	2·1	3·2	≤0·5	0·6

Normal reference basal and peak hormone levels, respectively are as follows: GH <5·0 and >7·0 μg/l; cortisol 140–690 and >500 nmol/l; prolactin <15 μg/l and >2·5 × basal level; LH (follicular phase) 2·0–12·0 IU/l (post-menopausal), >20·0 IU/l and 4–6 × basal level.

i.v.) administration. At 180 min, additional blood samples were collected from all patients for T3 measurement.

The rhythm of TSH secretion and the TSH response to TRH were re-evaluated in eight patients after 4–12 (median 9·5) months of hormone replacement therapy, according to the same protocol used before treatment. Hormone replacement therapy consisted of levothyroxine (2·0 μg/kg/day po) and prednisone (2·5–5 mg/day po) in all patients and oral oestrogens and progesterone in only two patients. All patients were clinically and biochemically euthyroid when re-evaluated.

Blood was collected in glass tubes, allowed to clot at room temperature and serum was separated after centrifugation at 2000 r.p.m. for 10 min. Serum samples were kept at −20°C until assayed.

Assays

Serum TSH was measured by an immunofluorimetric assay developed in our laboratory (Vieira *et al*., 1992). This assay employs an anti-β-TSH monoclonal antibody, with <1% cross-reactivity with FSH, LH and hCG, coupled to microtitre polyethylene plaques (antibody concentration 10 mg/l). Standard TSH was the 2nd International Research Preparation of human TSH (code 80/558 (1983); NIBSC, Potters Bar, UK) diluted in TSH-free human serum prepared by affinity chromatography in a Sepharose column coupled to the anti-β-TSH monoclonal antibody. A monoclonal antibody against the α subunit of the glycoprotein hormones was labelled with Europium and used as the second antibody, thus allowing the assay to detect only intact TSH. Fluorescence was measured in a time-resolved fluorometer (Delphia, Wallac, Finland). The sensitivity of this assay was 0·03–0·05 mU/l. The intra-assay coefficient of variation was <10% for measurements between 0·1 and 400 mU/l. The interassay coefficients of variation were 17·3, 10·1 and 11·4%, for mean TSH values of 0·82, 13·7 and 36·2 mU/l, respectively. All samples from the same patient or control were run within the same assay.

Serum levels of T3, T4, free T4 (fT4), PRL and LH were measured by immunofluorimetric assay kits (Delphia). GH was measured by an immunoenzymometric assay and cortisol by a radioimmunoassay according to previously described methods (Vieira *et al*., 1979, 1990).

Data analysis

In each patient or control, the mean afternoon and night TSH levels were calculated using the five values of TSH obtained at 30 min intervals between 1500 and 1700 h and between 0100 and 0300 h, respectively. The nocturnal per cent increment of TSH was calculated by the formula

$$[(\text{mean nocturnal TSH level} - \text{mean afternoon TSH level})/\text{mean afternoon TSH level}] \times 100$$

Basal TSH levels were considered the values of TSH obtained after an overnight fast, between 0800 and 0900 h, before TRH administration. The absolute TSH increment after TRH was calculated as the difference between the highest TSH value observed after TRH administration and the basal TSH value. The per cent TSH increment after TRH was calculated by dividing the absolute TSH increment by the basal TSH value and multiplying the result by 100.

Statistical analyses were performed using Student's *t*-test, Mann–Whitney *U* test, Wilcoxon signed rank test and linear regression analysis, as indicated. Statistical significance was set at $P \leq 0{\cdot}05$. Results are expressed as mean ± SE unless otherwise indicated.

Results

Thyroid hormones and basal and TRH-stimulated TSH levels before treatment

Laboratory evaluation of thyroid function of the 10 patients with Sheehan's syndrome before treatment is shown in Table 1. Total T4 and total T3 levels were usually very low in the patients as compared with the respective normal reference values (51–142 nmol/l and 1·2–3·4 nmol/l, respectively) or controls. Basal (morning) TSH levels were normal in seven and slightly elevated in three patients as compared with the normal range for TSH in our laboratory (0·3–4·0 mU/l). As a group, however, patients with Sheehan's syndrome had significantly higher basal TSH levels than controls (3·0 ± 0·9 (range 0·5–9·8) mU/l *vs* 0·7 ± 0·2 (range 0·3–1·6) mU/l, respectively, $P = 0·03$, Mann–Whitney). This difference remained significant even when the patient with positive thyroid antibodies and the highest TSH value was excluded from analysis (2·2 ± 0·5 *vs* 0·7 ± 0·2 mU/l, $P = 0·05$).

As shown in Table 1, peak TSH levels (4·3 ± 1·1 mU/l), absolute TSH increments (1·3 ± 0·3 mU/l) and per cent TSH increments (61%) after TRH in patients with Sheehan's syndrome were significantly reduced as compared with controls. Peak TSH levels in both patients and controls were found to occur at 15 or 30 min after TRH administration. T3 levels 180 min after TRH administration in patients with Sheehan's syndrome were not significantly different from their basal T3 levels (0·54 ± 0·16 and 0·69 ± 0·17 nmol/l, respectively).

Afternoon and nocturnal TSH levels before treatment

As shown in Fig. 1, mean afternoon TSH levels in patients with Sheehan's syndrome were significantly higher than in controls (3·3 ± 1·04 *vs* 0·5 ± 0·15 mU/l, $P = 0·002$, Mann–Whitney). This difference remained significant even when the only patient with positive thyroid antibodies, who also presented the highest TSH value, was excluded from analysis (2·4 ± 0·7 *vs* 0·5 ± 0·15 mU/l, $P = 0·006$). At night, mean TSH levels in patients with Sheehan's syndrome (3·3 ± 1·07 mU/l) remained virtually unchanged in relation to their afternoon values, whereas in control subjects they showed a significant rise from 0·5 ± 0·15 mU/l in the afternoon to 1·1 ± 0·34 mU/l ($P = 0·016$, Wilcoxon). Although mean night TSH levels in patients with Sheehan's syndrome were still higher than in controls, this difference did not reach statistical significance ($P = 0·193$, Mann–Whitney). As shown in Fig. 2, the mean nocturnal TSH increment in patients with Sheehan's syndrome was significantly blunted as compared with controls (−4·9% (range −34 to 27%) *vs* 143% (range 31–221%), $P = 0·0001$, Mann–Whitney).

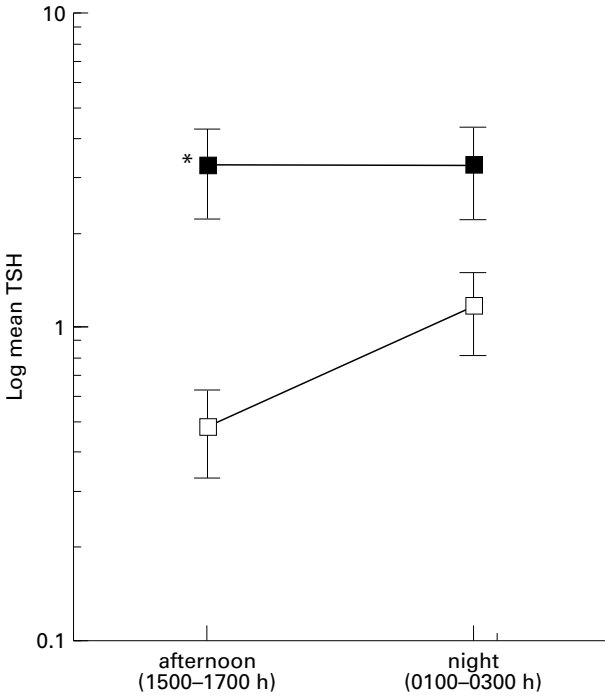

Fig. 1 Afternoon and night TSH levels. ■ patients with Sheehan's syndrome ($n = 10$) and □ controls ($n = 7$). Each square represents the mean of individual TSH means obtained from 5 measurements. Vertical bars represent the SEs. (*, $P = 0·002$, Mann–Whitney).

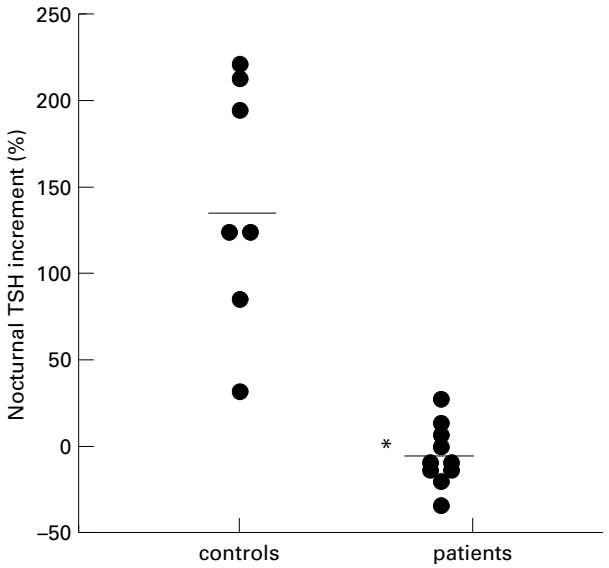

Fig. 2 Nocturnal TSH increments in patients with Sheehan's syndrome and controls. The magnitude of the nocturnal TSH surge is expressed as the percent increase in the mean night TSH value over the mean afternoon TSH values. Horizontal bars represent mean values. (*, $P = 0·0001$, Mann–Whitney).

Thyroid hormones and basal and TRH-stimulated TSH levels after treatment

In the eight patients who were re-evaluated during hormone replacement therapy, thyroid hormone levels rose significantly and reached the normal range of their respective reference values in all except one patient whose T_3 level was slightly low. Total T4 levels rose from 14·2 ± 1·3 to 97·2 ± 6·0 (range 78·5–132·6) nmol/l and total T3 levels rose from 0·60 ± 0·13 to 1·70 ± 0·18 (range 0·91–2·35) nmol/l after 4–12 months of treatment. Serum fT4 levels (14·7 ± 1·1 (range 10·3–20·6) pmol/l) were all within the normal reference range (7·7–26·0 pmol/l) and all patients were clinically euthyroid and presented no signs or symptoms of glucocorticoid excess or deficiency during hormone replacement therapy.

In these patients, basal (morning) TSH levels decreased significantly from 2·9 ± 1·13 mU/l before treatment to 0·16 ± 0·05 mU/l, or even less, during treatment ($P \leq 0{\cdot}008$), since morning TSH values equal to or below assay sensitivity occurred in four patients and were assigned a value equal to the assay sensitivity for statistical calculations.

Peak TSH levels after TRH decreased significantly from 4·16 ± 1·4 to 0·72 ± 0·27 mU/l during hormone replacement therapy ($P = 0{\cdot}0078$, Wilcoxon). The mean peak TSH level after TRH in patients during treatment (0·72 mU/l) was 14-fold lower than the mean peak TSH level after TRH observed in controls (10·6 mU/l).

There were strong positive correlations between pre- and post-treatment basal TSH levels ($r = 0{\cdot}82$, $P = 0{\cdot}012$) and between pre- and post-treatment peak TSH levels after TRH administration ($r = 0{\cdot}91$, $P = 0{\cdot}0017$). No significant correlations were found between pre- or post-treatment TSH levels (basal and peak) and the respective pre- or post-treatment thyroid hormone levels.

TSH rhythm during treatment

Among the eight patients re-evaluated for TSH rhythm during hormone replacement therapy, two patients were excluded from analysis because their afternoon and night TSH levels were both below the sensitivity of our assay. In the remaining six patients, the mean pretreatment afternoon and night TSH levels were 3·46 ± 1·65 and 3·26 ± 1·55 mU/l, respectively, which resulted in a mean nocturnal TSH surge of −7% (range −20 to 13%). During treatment, mean afternoon and night TSH levels in these patients decreased significantly to 0·29 ± 0·07 and 0·48 ± 0·21 mU/l, respectively ($P = 0{\cdot}03$, Wilcoxon), resulting in a mean nocturnal TSH surge of 64% (range 39 to 231%).

Although the mean nocturnal TSH surge increased from −7% to 64% after treatment in these patients, the difference did not reach statistical significance ($P = 0{\cdot}16$, Wilcoxon). However, the 64% increment of nocturnal TSH during treatment was not significantly different from the 142% increment observed in controls ($P = 0{\cdot}18$, Mann–Whitney).

An individual analysis of these increments shows that two patients failed to exhibit a normal nocturnal increase in TSH after treatment, whereas four patients increased their nocturnal TSH surges to values within the range observed in controls (Fig. 3). No differences were found in clinical or laboratory data between patients who failed to normalize the nocturnal TSH surge and those who presented a normal nocturnal TSH surge during treatment.

Discussion

In this study, TSH levels in patients with post-partum panhypopituitarism were shown to be elevated and to lack the characteristic nocturnal surge observed in normal subjects. Although similar findings have been reported in patients with central hypothyroidism due to various other hypothalamo-pituitary diseases (Patel & Burger, 1973; Petersen *et al*., 1978; Faglia *et al*., 1979; Beck-Peccoz *et al*., 1985; Caron *et al*., 1986; Rose *et al*., 1990), our results of increased TSH levels in post-partum panhypopituitarism specifically agree with the only report of TSH levels in a comparable group of patients (Isotani *et al*., 1988). No previous study has evaluated the rhythm of TSH secretion in this condition.

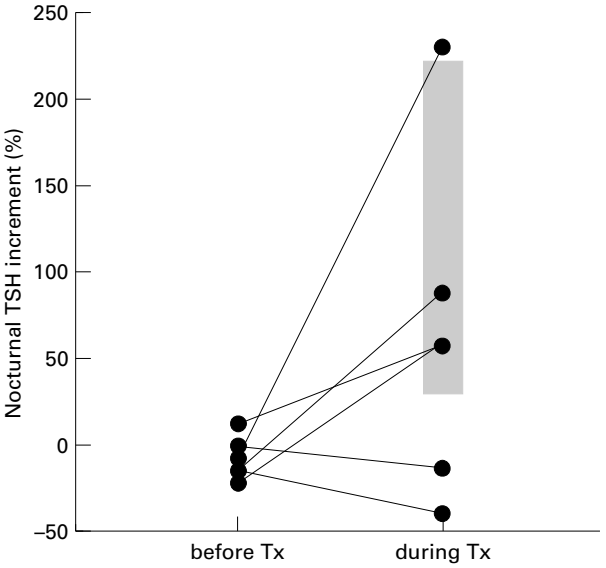

Fig. 3 Individual nocturnal TSH increments in 6 patients with Sheehan's syndrome before and during replacement therapy with thyroxine and glucocorticoid (Tx). The magnitude of the nocturnal TSH surge is expressed as the percent increase in the mean night TSH value over the mean afternoon TSH value. The shaded area represents the range of nocturnal TSH increments observed in normal controls.

The identity of circulating TSH was based on an ultrasensitive 'sandwich' immunofluorimetric assay with two monoclonal antibodies directed at separate epitopes, each in one subunit of the TSH molecule, so that all immunoactive TSH measured was the $\alpha\beta$ heterodimer and none of the free α or β TSH subunits (Vieira *et al*., 1992). In spite of the empty sella found in all patients studied, the pituitary origin of circulating TSH in these patients is strongly suggested by the consistent, albeit small, TSH responses after TRH administration, as well as by the marked fall in TSH levels during hormone replacement therapy with thyroxine and glucocorticoid.

The increased TSH levels observed in our patients are more likely to result from increased pituitary secretion than from decreased metabolic clearance of TSH. This view is supported by previous studies showing a 40% decrease in the metabolic clearance rate of TSH in hypothyroidism (Ridgway *et al*., 1974), which could not account for the more than four-fold increase in TSH levels observed in our group of patients.

In order to investigate whether the loss of TSH rhythm in Sheehan's syndrome resulted from the hormonal status of the patients or from an irreversible hypothalamic lesion, TSH rhythm was re-evaluated after treatment. As already described in patients with central hypothyroidism receiving thyroxine (Isotani *et al*., 1988), basal TSH levels fell markedly below the normal range in nearly all patients with Sheehan's syndrome during thyroxine and glucocorticoid replacement. This was not due to overtreatment because free thyroxine levels were all within the mid-normal range and no signs or symptoms of thyroid hormone or glucocorticoid excess were detected in these patients. Since a normal TSH rhythm could be demonstrated during treatment in most patients whose TSH levels were still measurable, the loss of the nocturnal TSH surge observed before treatment in these patients was probably determined by their marked hypothyroidism, similar to the loss of TSH rhythm found in severe primary hypothyroidism (Adriaanse *et al*., 1992a, b).

The persistent lack of the nocturnal TSH surge after hormone replacement therapy observed in two patients who did not present any of the non-thyroidal conditions known to blunt the nocturnal TSH surge, like diabetes mellitus (Bartalena *et al*., 1993), glucocorticoid excess (Bartalena *et al*., 1991), or endogenous depression (Bartalena *et al*., 1990), suggests that post-partum hypothalamic damage may have caused abnormal TSH rhythmicity in these patients. Destruction of TRH-secreting paraventricular neurons and/or disruption of their connections with hypothalamic and extrahypothalamic structures responsible for TSH circadian rhythm could have irreversibly abolished the nocturnal TSH surge in these patients. Interestingly, necropsy findings of the hypothalamus in Sheehan's syndrome show substantial atrophy of the supraoptic nuclei and a less marked atrophy of the paraventricular nuclei (Whitehead, 1963). The functional correlate of these marked atrophic changes in the supraoptic nuclei is probably the decreased vasopressin reserve found in Sheehan's syndrome (Iwasaki *et al*., 1989; Arnaout & Ajlouni, 1992). Likewise, the lack of the nocturnal surge of TSH after hormone replacement could reflect permanent damage of the paraventricular nuclei of the hypothalamus.

It has been proposed that the loss of the nocturnal TSH surge could account for decreased thyroid function in patients with central hypothyroidism (Caron *et al*., 1986; Rose *et al*., 1990). In support of this hypothesis, free T4 levels in patients with hypothalamo-pituitary disease and absent nocturnal TSH surge have been shown to be significantly lower as compared with patients with a normal nocturnal TSH rise (Rose *et al*., 1990). On the other hand, although the nocturnal TSH surge accounts for a substantial amount of the 24 h TSH secretion in normal subjects, no corresponding increases in thyroid hormone levels have been found following the nocturnal TSH rise (Goichot *et al*., 1994). Furthermore, a recent study has shown that nocturnal TSH has altered glycosylation and reduced 'in vitro' bioactivity as compared with TSH secreted during the daytime (Persani *et al*., 1995). At any rate, considering that TSH levels in Sheehan's syndrome are increased throughout the 24 h period, the lack of a further nocturnal increment would appear quantitatively unimportant and unlikely to contribute to the development of hypothyroidism in these patients.

The apparent discrepancy posed by the observation of normal or increased instead of decreased TSH levels in central hypothyroidism is even more intriguing in Sheehan's syndrome in view of the massive pituitary necrosis that causes this condition. Virtually no pituitary remnant could be found within the sella on CT scan but, in a few patients submitted to magnetic resonance imaging, a very thin band of pituitary tissue could be seen on the floor of the sella.

Given the 14-fold higher TSH peak after TRH in controls as compared with Sheehan's patients during hormone replacement treatment, we estimated that the mean functional thyrotroph population in our patients was reduced to about 7% of its original size. The rationale for this comparison is that patients with Sheehan's syndrome receiving hormone replacement therapy and normal controls have comparable degrees of hypothalamo-pituitary inhibition by circulating thyroid and glucocorticoid hormones. Thus, the ratio of the TRH-induced TSH peaks between controls and patients should reflect the sizes of their functional thyrotroph populations. The predominant role of the remaining thyrotroph mass as compared with the circulating thyroid hormone levels in determining the level of TSH secretion in patients with Sheehan's syndrome is further supported by the strong positive correlations found between pre- and post-treatment TSH levels, whereas no

significant correlations were found between TSH and thyroid hormone values in this study.

However, our findings of increased TSH secretion and loss of TSH rhythm in Sheehan's syndrome may represent a late development after pituitary necrosis. Theoretically, the expected sequence of events affecting the hypothalamo-pituitary-target gland axes following post-partum pituitary necrosis should start with a marked decrease in the serum concentrations of pituitary hormones followed by declining levels of pituitary-dependent hormones from the target glands. Declining levels of circulating thyroid hormones would, in turn, stimulate TSH synthesis and secretion in the remaining thyrotrophs by acting both directly, at the pituitary level, and indirectly, at the hypothalamic paraventricular nuclei, to promote increased TRH synthesis and secretion (Segerson *et al*., 1987; Dyess *et al*., 1988; Shupnik *et al*., 1989). In addition, the low levels of cortisol as well as a possible decrease in hypothalamic somatostatin due to decreased GH could contribute to further increase TSH secretion in these patients (Wilbur & Utiger, 1969; Arimura & Schally, 1976; Re *et al*., 1976).

If the above sequence of events really takes place in patients with long-standing Sheehan's syndrome, the secretory activity of the remaining thyrotrophs, under conditions of increased TRH stimulation and decreased circulating thyroid hormone levels, would be nearly maximal and similar to severe hypothyroidism. In accordance with this idea, loss of TSH response to TRH and of the nocturnal TSH rise are both common to Sheehan's syndrome and severe primary hypothyroidism but do not occur in mild or moderate primary hypothyroidism (Adriaanse *et al*., 1992a, b).

Why increased TSH secretion fails to increase thyroid hormone levels in the absence of intrinsic thyroid disease in patients with Sheehan's syndrome is an apparent paradox that could be solved in two different ways. First, although no study has yet addressed the question of TSH bioactivity in this condition, it could be argued that decreased TSH bioactivity is the cause of hypothyroidism in Sheehan's syndrome. Nevertheless, it should be noted that the decreased TSH bioactivity reported in patients with central hypothyroidism is probably due to TRH deficiency, since TRH administration was able to increase TSH levels and TSH bioactivity in these patients (Faglia *et al*., 1983; Beck-Peccoz *et al*., 1985; Weintraub *et al*., 1989). In contrast, TRH administration to our patients caused only minimal TSH increments and no change in circulating T3 levels. Furthermore, when TRH is infused for 24 hours in Sheehan's patients, no significant changes are observed in TSH or fT4 levels (Maccagnan & Abucham, unpublished data).

Second, if TSH bioactivity is preserved in Sheehan's syndrome, increasing TSH secretion in response to the low levels of circulating T4 would tend to increase the low T4 levels. However, as T4 starts to increase, thyrotrophs would, in turn, start to decrease TSH secretion. Considering the markedly reduced population of thyrotrophs in Sheehan's syndrome, the expected TSH-lowering effect of similar increases in T4 levels should be much greater in hypothyroid Sheehan's patients than in primary hypothyroidism patients. Indeed, normalization of fT4 levels to the mid-normal range during hormone replacement therapy reduced TSH levels to low or undetectable levels in all but one of our patients, whereas physiological T4 replacement in primary hypothyroid patients decreases TSH levels to the normal range. In addition, since those oscillations of circulating T4 and TSH in patients with Sheehan's syndrome would occur within the subnormal range of thyroxine levels where the dose–response curve of thyrotrophin inhibition by T4 is very steep (Reichlin & Utiger, 1967), a vicious cycle would be generated, preventing normalization of T4 levels in these patients. Which of these two mechanisms accounts for increased TSH levels and hypothyroidism in patients with Sheehan's syndrome remains to be determined.

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References

Adriaanse, R., Romijn, J.A., Endert, E. & Wiersinga, W.M. (1992a) The nocturnal thyroid-stimulating hormone surge is absent in overt, present in mild primary and equivocal in central hypothyroidism. *Acta Endocrinologica (Copenh)*, **126,** 206–212.

Adriaanse, R., Brabant, G., Prank, K., Endert, E. & Wiersinga, W.M. (1992b) Circadian changes in pulsatile TSH release in primary hypothyroidism. *Clinical Endocrinology*, **37,** 504–510.

Arimura, A. & Schally, A.V. (1976) Increases in basal and thyrotropin-releasing hormone-stimulated secretion of thyrotropin (TSH) by passive immunization with antiserum to somatostatin in rats. *Endocrinology*, **98,** 1069–1072.

Arnaout, M.A. & Ajlouni, K. (1992) Plasma vasopressin responses in postpartum hypopituitarism: impaired response to osmotic stimuli. *Acta Endocrinologica (Copenh)*, **127,** 494–498.

Bartalena, L., Placidi, G.F. Martino, E., Falcone, M., Pellegrini, L., Dell'Osso, L., Pacchiarotti, A. & Pinchera, A. (1990) Nocturnal serum thyrotropin (TSH) surge and the TSH response to TSH-releasing hormone: dissociated behavior in untreated depressives. *Journal of Clinical Endocrinology and Metabolism*, **71,** 650–655.

Bartalena, L., Martino, E., Petrini, L., Velluzzi, F., Loviselli, A., Grasso, L., Mammoli, C. & Pinchera, A. (1991) The nocturnal serum thyrotropin surge is abolished in patients with adrenocorticotropin (ACTH)-dependent or ACTH-independent Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism*, **72,** 1195–1199.

Bartalena, L., Cossu, E., Grasso, L., Velluzzi, E., Loviselli, A., Cirillo, R. & Martino, E. (1993) Relationship between serum thyrotropin peak and metabolic control in diabetic patients. *Journal of Clinical Endocrinology and Metabolism*, **76,** 983–987.

Beck-Peccoz, P., Amr, S., Menezes-Ferreira, M., Faglia, G. &

Weintraub, B.D. (1985) Decreased receptor binding of biologically inactive thyrotropin in central hypothyroidism. *New England Journal of Medicine*, **312,** 1085–1090.

Brabant, G., Ranft, U., Ocran, K., Hesch, R.D. & von zur Muhlen, A. (1986) Thyrotropin an episodically secreted hormone. *Acta Endocrinologica (Copenh)*, **112,** 315–322.

Brabant, G., Prank, K., Ranft, U., Schuermeyer, Th., Wagner, T.O.F., Hauser, H., Kummer, B., Feistner, H., Hesch, R.D. & von zur Muhlen, A. (1990) Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. *Journal of Clinical Endocrinology and Metabolism*, **70,** 403–409.

Brabant, G., Prank, K., von zur Muhlen, A., Hoang-Vu, C., Hesch, R.D. & von zur Muhlen, A. (1991) Hypothalamic regulation of pulsatile thyrotropin secretion. *Journal of Clinical Endocrinology and Metabolism*, **72,** 145–150.

Caron, P.J., Nieman, L.K., Rose, S.R. & Nisula, B.C. (1986) Deficient nocturnal surge of thyrotropin in central hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*, **62,** 960–964.

Dyess, E.M., Segerson, T.P., Liposits, Z., Paull, W.K., Kaplan, M.M., Wu, P., Jackson, I.M. & Lechan, R.M. (1988) Triiodothyronine exerts direct cell-specific regulation of thyrotropin-releasing hormone gene expression in the hypothalamic paraventricular nucleus. *Endocrinology*, **123,** 2291–2297.

Faglia, G., Bitensky, L., Pinchera, A., Ferrari, C., Paracchi, A., Beck-Peccoz, P., Ambrosi, B. & Spada, A. (1979) Thyrotropin secretion in patients with central hypothyroidism: Evidence for reduced biological activity of immunoreactive thyrotropin. *Journal of Clinical Endocrinology and Metabolism*, **48,** 989–998.

Faglia, G., Beck-Peccoz, P., Ballabio, M. & Nava, C. (1983) Excess of beta-subunit of thyrotropin (TSH) in patients with idiopatic central hypothyroidism due to secretion of TSH with reduced biological activity. *Journal of Clinical Endocrinology and Metabolism*, **56,** 908–914.

Fukuda, H. & Greer, M.A. (1975) The effect of basal hypothalamic deafferentation on nyctohemeral rhythm of plasma TSH. *Endocrinology*, **97,** 749–755.

Goichot, B., Brandenberger, G., Saini, S., Wittersheim, G. & Follenius, M. (1994) Nycthemeral patterns of thyroid hormones and their relationships with thyrotropin variations and sleep structure. *Journal of Endocrinological Investigation*, **17,** 181–187.

Greenspan, S.L., Klibanski, A., Schoenfeld, D. & Ridgway, E.C. (1986) Pulsatile secretion of thyrotropin in man. *Journal of Clinical Endocrinology and Metabolism*, **63,** 661–668.

Isotani, H., Takamatsu, J., Kitaoka, H., Ikegami, Y., Majima, T., Sakane, S., Majima, M., Takeda, K. & Mozai, T. (1988) Serum thyrotropin concentrations in patients with Sheehan's syndrome: reevaluation of the usefulness in the diagnosis. *Nippon-Naibunpi-Gakkai-Zasshi*, **64,** 22–30.

Iwasaki, Y., Oiso, Y., Londo, K., Yamauchi, K., Takatsuki, K., Kondo, K., Hasegawa, H., Itatsu, T., Niinomi, M. & Tomita, A. (1989) Neurohypophyseal function in post-partum hypopituitarism: impaired plasma vasopressin response to osmotic stimuli. *Journal of Clinical Endocrinology and Metabolism*, **68,** 560–565.

Morley, J.E. (1981) Neuroendocrine control of thyrotropin secretion. *Endocrine Reviews*, **2,** 396–436.

Patel, Y.C. & Burger, H.G. (1973) Serum thyrotropin (TSH) in pituitary and/or hypothalamic hypothyroidism: normal or elevated basal levels and paradoxical responses to thyrotropin-releasing hormone. *Journal of Clinical Endocrinology and Metabolism*, **37,** 190–196.

Patel, Y.C., Alford, F.P. & Burger, H.G. (1972) The 24-hour plasma thyrotrophin profile. *Clinical Science*, **43,** 71–77.

Persani, L., Terzolo, M., Asteria, C., Orlandi, F., Angeli, A. & Beck-Peccoz, P. (1995) Circadian variations of thyrotropin bioactivity in normal subjects and patients with primary hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*, **80,** 2722–2728.

Petersen, V.B., McGregor, A.M., Belchetz, P.E., Elkeles, R.S. & Hall, R. (1978) The secretion of thyrotrophin with impaired biological activity in patients with hypothalamic-pituitary disease. *Clinical Endocrinology*, **8,** 397–402.

Re, R.N., Kourides, I.A., Ridgway, E.D., Weintraub, B.D. & Maloof, F. (1976) The effect of glucocorticoid administration on human pituitary secretion of thyrotropin and prolactin. *Journal of Clinical Endocrinology and Metabolism*, **43,** 338–346.

Reichlin, S. & Utiger, R. (1967) Regulation of the pituitary-thyroid axis in man: Relationship of TSH concentration to concentration of free and total thyroxine in plasma. *Journal of Clinical Endocrinology and Metabolism*, **27,** 251–255.

Ridgway, E.C., Weintraub, B.D. & Maloof, F. (1974) Metabolic clearance and production rates of human thyrotropin. *Journal of Clinical Investigation*, **53,** 895–903.

Rose, S.R., Manasco, P.K., Pearce, S. & Nisula, B.C. (1990) Hypothyroidism and deficiency of nocturnal thyrotropin surge in children with hypothalamic-pituitary disorders. *Journal of Clinical Endocrinology and Metabolism*, **70,** 1750–1755.

Segerson, T.P., Kauer, J., Wolfe, H.C., Mobtaker, H., Wu, P., Jackson, I.M. & Lechan, R.M. (1987) Thyroid hormone regulates TRH biosynthesis in the paraventricular nucleus of the rat hypothalamus. *Science*, **238,** 78–80.

Sheehan, H.L. & Murdoch, R. (1939) Post-partum necrosis of anterior pituitary. *Lancet*, **8,** 818–820.

Sheehan, H.L. & Whitehead, R. (1963) The neurohypophysis in post-partum hypopituitarism. *Journal of Pathology and Bacteriology*, **85,** 145–167.

Shupnik, M.A., Ridgway, E.C. & Chin, W.W. (1989) Molecular biology of thyrotropin. *Endocrine Reviews*, **10,** 459–475.

Vieira, J.G.H., Russo, E.M.K., Germek, O.A. & Antunes, L.N. (1979) Método radioimunológico para a dosagem do cortisol sérico. *Revista Brasileira de Patologia Clínica*, **15,** 125–130.

Vieira, J.G.H., Lombardi, M.T. & Nishida, S.K. (1990) Monoclonal antibody-based immunoenzymometric assay for serum human growth hormone. *Brazilian Journal of Medical and Biological Research*, **23,** 293–296.

Vieira, J.G.H., Kunii, I.S., Nishida, S.K., Matsumura, L.K., Russo, E.M.K. & Maciel, R.M.B. (1992) Desenvolvimento e aplicação de um método imunofluorimétrico para a dosagem de tireotrofina humana (TSH) no soro e em sangue total colhido em papel de filtro. *Arquivos Brasileiros de Endocrinologia e Metabologia*, **36,** 7–12.

Weeke, J. (1973) Circadian variation of the serum thyrotropin levels in human subjects. *Scandinavian Journal of Clinical and Laboratory Investigation*, **31,** 337–342.

Weeke, J. & Gundersen, J.G. (1978) Circadian and 30 minutes variations in serum TSH and thyroid hormones in normal subjects. *Acta Endocrinologica (Copenh)*, **89,** 659–672.

Weintraub, B.D., Gesundeheit, N., Taylor, T. & Gyves, P.W. (1989) Effect of TRH on glycosylation and biological action. *Annals of the New York Academy of Sciences*, **553,** 205–213.

Whitehead, R. (1963) The hypothalamus in post-partum hypopituitarism. *Journal of Pathology and Bacteriology*, **86,** 55–67.

Wilbur, J.F. & Utiger, R.D. (1969) The effect of glucocorticoids on thyrotropin secretion. *Journal of Clinical Investigation*, **48,** 2096–2103.