Thyrotropin-Secreting Pituitary Adenomas: Report of Seven Cases

ALBERT BECKERS, ROGER ABS, CHARLES MAHLER, JEAN-LOUIS VANDALEM*, GUY PIRENS, GEORGES HENNEN, AND ACHILLE STEVENAERT

Departments of Endocrinology (A.B., J.-L.V., G.P., G.H.) and Neurosurgery (A.S.), University of Liège, Liège; and the Department of Endocrinology, University of Antwerp (R.A.), and Middelheim Hospital of Antwerp (C.M.), Antwerp, Belgium.

ABSTRACT. Seven patients with hyperthyroidism due to a TSH-secreting pituitary macroadenoma have been observed over a period of 15 yr. Serum TSH levels varied between 1.1–36.3 mU/L. The serum α-subunit level was low in 1 case, while in 4 other cases the concentration was elevated and varied between 3.7–7.8 μg/L. Serum TSHβ levels were normal in the 4 cases in which it was determined. Serum GH or PRL levels were elevated in 5 cases. In 1 patient the cosecretion of TSH, GH, and PRL was confirmed by immunochemical examination. Serum TSH and α-subunit responses to TRH, GnRH, CRF, GRF, desmopressin, methimazole, T3, and bromocriptine administration were variable when studied. Serum TSH and α-subunit circadian rhythms were absent in 1 case and inverted in another. A serum α-subunit pulsatility without TSH pulses was observed in 1 patient. Five patients underwent transphenoidal adenomectomy. Three of 4 patients operated on in our center were cured, but a recurrence of the adenoma was found in 1 of them after 5 yr. The fifth patient was not cured. Treatment with octreotide in 3 patients resulted in normalization of serum TSH, GH, and thyroid hormones levels. Cosecretion of PRL in 1 case and α-subunit in 2 cases was also inhibited. Partial tachyphylaxis occurred in 1 patient. In summary, heterogeneity in clinical presentation, hormonal expression, and therapeutic response appears to characterize these TSH-secreting adenomas. (J Clin Endocrinol Metab 72: 477–483, 1991)

INAPPROPRIATE secretion of TSH by the pituitary is a rare disorder, characterized by unsuppressed TSH levels in spite of elevated serum thyroid hormone concentrations. It is encountered in the syndrome of selective pituitary resistance to thyroid hormone action or results from a TSH-secreting pituitary tumor. Two review articles mentioned the existence of 70 cases of TSH-secreting adenomas (1, 2). The largest primary series, consisting of 9 patients, was reported recently (3). We add here 7 new cases with detailed hormonal investigations. Neurosurgical results in 5 patients and long term effects of octreotide in 3 patients are reported.

Subjects and Methods

Patients

Seven patients (four females and three males) with TSH-secreting pituitary adenomas are documented. Medical history, clinical characteristics, and hormonal data are summarized in Table 1. All patients presented with a goiter and hyperthyroidism. Two patients (no. 1 and 3) were previously considered as suffering from primary hyperthyroidism and were treated with methimazole for 2 yr; one of them subsequently underwent thyroidectomy. Three patients with mild (no. 2 and 6) or pronounced (no. 7) clinical signs of acromegaly showed elevated GH and insulin-like growth factor-I (IGF-I) levels. Three patients (no. 1–3) showed hyperprolactinemia. One patient (no. 5) presented with visual field defects. One patient (no. 2) was partially reported previously (4). In four patients (no. 1, 2, 4, and 5) transphenoidal surgery was performed by one of us (A.S.) according to a previously described technique (5).

Asays

Serum TSH levels were measured using a RIA kit (Techland, Liège, Belgium). Serum α-subunit and TSHβ concentrations were measured using a RIA developed in our laboratory. The bound/free separation was achieved by using specific precipitation with an antirabbit antibody. The sensitivity was 0.1 μg/L for the two systems. The intraassay coefficient of variation was between 2–8% at doses ranging from 0.5–5 μg/L for the α-subunit system and between 2–10% at doses ranging from 0.5–12 μg/L for the TSHβ system. The interassay coefficient of variation for the α-subunit assay was 7.4% at a dose of 0.8 μg/L, 5.0% at a dose of 2 μg/L, and 9.4% at a dose of 5 μg/L. Other pituitary hormones (GH, PRL, LH, and FSH) and total thyroid hormone concentrations were measured using commercial kits. Serum free thyroid hormones were determined using the Le-petit-Sclavo kit (Milan, Italy). Plasma IGF-I levels were as-
Table 1. Clinical and endocrinological data

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>(4)</th>
<th>(5)</th>
<th>(6)</th>
<th>(7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)/sex</td>
<td>49/F</td>
<td>34/F</td>
<td>55/F</td>
<td>55/M</td>
</tr>
<tr>
<td>Grading/tumor diameter (mm)</td>
<td>IIA/12</td>
<td>IIA/14</td>
<td>IIIA/18</td>
<td>IIIA/18</td>
</tr>
<tr>
<td>TT4 (1.2–3.4 nmol/L)</td>
<td>4.0</td>
<td>5.2</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>TT4 (51–142 nmol/L)</td>
<td>32</td>
<td>39</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>fT3 (3–9 pmol/L)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>TSH (0.1–4.5 mU/L)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>α-Subunit (0.1–1.3 µg/L)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>TSHβ (0.1–0.8 µg/L)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>α-Subunit/TSH molar ratio</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>PRL/after TRH (&lt;20 µg/L)</td>
<td>7/12</td>
<td>9/12</td>
<td>6/9</td>
<td>6/8</td>
</tr>
<tr>
<td>GH (0.6–6.5 µg/L)</td>
<td>2.0</td>
<td>3.9</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>IGF-I (0.1–2.2 µu/mL)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>TRH/α-subunit response (%) (*) to TRH</td>
<td>0/ND</td>
<td>+69/0</td>
<td>+20/ND</td>
<td>+104/+73</td>
</tr>
<tr>
<td>GnRH</td>
<td>ND/ND</td>
<td>0/0</td>
<td>ND/ND</td>
<td>0/+53</td>
</tr>
<tr>
<td>CRF</td>
<td>ND/ND</td>
<td>+11/0</td>
<td>ND/ND</td>
<td>ND/ND</td>
</tr>
<tr>
<td>GRF</td>
<td>ND/ND</td>
<td>0/0</td>
<td>ND/ND</td>
<td>ND/ND</td>
</tr>
<tr>
<td>Deramethasone</td>
<td>ND/ND</td>
<td>ND/ND</td>
<td>ND/ND</td>
<td>ND/ND</td>
</tr>
<tr>
<td>Methimazole</td>
<td>+/ND</td>
<td>+/ND</td>
<td>+/ND</td>
<td>+/ND</td>
</tr>
<tr>
<td>T2</td>
<td>+/ND</td>
<td>+/ND</td>
<td>+/ND</td>
<td>+/ND</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>-/ND</td>
<td>-/ND</td>
<td>-/ND</td>
<td>-/ND</td>
</tr>
<tr>
<td>Octreotide</td>
<td>-100/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgery (82), methimazole (74–76), octreotide (76–82)</td>
<td>Surgery (82), methimazole (73–75), surgery (76–82), radiotherapy (82)</td>
<td>Surgery (83), surgery (82), radiotherapy (84)</td>
<td>Surgery (82), methimazole (85), surgery (82)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Cured</td>
<td>Cured</td>
<td>Lost to follow-up</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Well controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND, Not done; TT4, total T4; fT3, free T3; +, positive; −, negative.

* Percent increase (+) or decrease (−) from baseline value.

sayed using a commercial kit (Nichols, San Juan Capistrano, CA). The α-subunit/TSH molar ratio was calculated on the basis of the following mol wt values: TSH, 28,000; and α-subunit, 14,700 (1 ng TSH corresponding to 3.228 µU).

Endocrine studies

The stimulatory effects of 200 µg TRH, iv, on TSH and α-subunit secretion were studied in all patients. A 100-µg GnRH iv test in five patients (no. 2 and 4–7) and a 50-µg CRF iv test and a 80-µg GRF iv test in three patients (no. 2, 5, and 6) were performed to evaluate a paradoxical release of TSH and α-subunit. The inhibitory effects on TSH and α-subunit secretion were studied. A demethasone test (four doses of 0.5 mg/day, orally, for 3 days) was performed in two patients (no. 4 and 5). Methimazole was given in doses varying from 10–60 mg daily during 1 yr in one patient (no. 4) and during 2 yr in two patients (no. 1 and 3) and in a dose of 60 mg daily during 1 month in one patient (no. 5). In three patients (no. 1, 3, and 5) 75 µg T2 were given daily during 10 days. The acute response to 5 µg bromocriptine orally was studied in four patients (no. 2 and 4–6). The acute response to 100 µg octreotide, sc, was studied in three patients (no. 2, 6, and 7).

Circadian rhythms of serum TSH and α-subunit were studied in two patients (no. 5 and 6) by sampling at 2-h intervals over a 24-h period. Serum TSH and α-subunit pulsatility was studied by sampling at 15-min intervals over an 8-h period in one patient (no. 6). Significant TSH and α-subunit peaks were identified with the Pulsar program (6). In two patients (no. 4 and 5) the decreases in serum TSH, α-subunit, and thyroid hormone levels after neurosurgery were recorded.

Immunocytochemistry

Tumor specimens were available for microscopic studies in five patients (no. 1–5) and for immunocytochemistry in four...
patients (no. 2-5). The peroxidase-antiperoxidase immunocytochemical method was applied to pituitary slices, as previously described, using antisera specific to LH, FSH, TSH, GH, PRL, and ACTH (7).

Octreotide treatment

Three patients were treated with octreotide (Sandostatin, Sandoz Ltd., Basel, Switzerland) during a period of 1 (no. 7) and 2 yr (no. 2 and 6). In two patients (no. 2 and 7) the daily dose was three doses of 100 μg, sc, whereas in one patient (no. 6) the dose was increased to three doses of 500 μg after 6 months because of tachyphylaxis. Follow-up was performed by measuring pituitary and thyroid hormones. In two patients (no. 2 and 6) tumor size was, respectively, evaluated by computed tomographic (CT) scanning and magnetic resonance (MR) imaging before and after 6 months and 1 yr of treatment.

Results

Clinical and endocrinological data (Table 1)

Hyperthyroidism was determined in all patients by means of elevated total or free thyroid hormone levels. Serum TSH levels varied between 1.1-36.3 mU/L. Serum α-subunit levels were elevated in four patients and low in one. Serum TSHβ levels were normal in the four patients where it was determined. TRH provoked an increase in serum TSH concentration greater than 100% from the baseline level in one patient only and between 20-80% in three patients, whereas no response was observed in the three remaining patients. α-Subunit secretion was moderately stimulated by TRH in two patients. A slight increase in serum TSH levels after GnRH treatment was observed in one patient only, whereas serum α-subunit levels increased over 50% in three patients. No paradoxical TSH release was observed after GRF or CRF injection. Dexamethasone did not modify TSH or α-subunit serum levels. Administration of methimazole resulted in a further elevation of serum TSH levels. T₃ did not suppress serum TSH levels. A significant TSH inhibition was obtained after bromocriptine administration in one patient and after octreotide administration in three patients. Concomitant elevated serum GH and IGF-I levels were found in three patients. A paradoxical release of GH after TRH treatment was observed in two of them (no. 2 and 6) and after CRF in one of them (no. 2). The elevated serum PRL concentration found in three patients could not be stimulated by TRH. In one patient (no. 2) the elevated levels of GH and PRL were partly suppressed by bromocriptine. Pituitary-gonadal and pituitary-adrenal axes were normal in all patients.

Rhythm

The study of circadian rhythm in patient 5 revealed the presence of a simultaneous acrophase in the secretion of TSH and α-subunit in the middle of the day (Fig. 1A).

![Graph A](image)

![Graph B](image)

**Fig. 1.** Study of circadian rhythm of pituitary hormones in two patients with TSH-secreting pituitary adenomas (A, patient 6; B, patient 6).

No circadian variations were observed in the secretory pattern of TSH and α-subunit in patient 6 (Fig. 1B). However, this acromegalic patient showed a circadian rhythm for GH secretion with the acrophase in the evening and during the night.

In patient 6 a pulsatile secretory pattern was observed for α-subunit, with three peaks over an 8-h period, but no pulses were recorded for TSH. The pulsatility of LH was preserved, but the timing and frequency of the α-subunit peaks did not correspond to those of the LH peaks (Fig. 2).

Neurosurgical treatment

Four of the five patients (no. 1, 2, 4, and 5) underwent transphenoidal adenectomy in our center. This resulted immediately after the operation in normalization of all hormonal parameters in all patients (Fig. 3, A and B; patient 5). However, secondary to the invasion of the sinus cavernous, an increase in serum TSH and thyroid hormone concentrations was observed in one patient (no. 4) 10 days after surgery (Fig. 3, C and D; patient 4).
5, of TSH and PRL cells in patient 3, and of TSH, GH, and PRL cells in patient 2.

**Octreotide treatment**

Acute administration of octreotide in three patients resulted in a pronounced suppression of serum TSH and, to a lesser degree, of α-subunit levels. In patient 2 serum PRL and GH levels also normalized with the first injection. Long term treatment with octreotide in patient 2 remained effective in normalizing pituitary and thyroid function for 2 yr. A CT scan performed after 1 yr of treatment revealed a pronounced decrease in tumor size (4). In patient 6 a normalization of all elevated hormone levels was obtained with a daily dose of three doses of 0.1 mg octreotide. After 6 months of treatment, increases in serum TSH, α-subunit, and GH concentrations were observed in spite of an adjustment of the dose to three doses of 0.5 mg/day (Fig. 4). However, thyroid function and IGF-I levels remained within normal limits; MR imaging performed after 6 months showed a 30% reduc-

---

**Fig. 2.** Study of pulsatility of pituitary hormones in a patient (no. 6) with a TSH-secreting pituitary adenoma. Arrows indicate serum α-subunit peaks, and asterisks indicate LH peaks.

Another patient (no. 2) showed a recurrence of the adenoma 5 yr after surgery, but a second operation corrected all abnormalities. Immunocytochemical examination revealed the presence of only TSH cells in patients 4 and

**Fig. 3.** Postoperative course of pituitary and thyroid hormones in two patients with TSH-secreting pituitary adenomas (A and B, patient 5; C and D, patient 4). fT3, Free T3; fT4, free T4.
TSH-SECRETING PITUITARY ADENOMAS

Fig. 4. Long term follow-up of hormonal parameters in a patient (no. 6) with a TSH-secreting pituitary adenoma receiving octreotide treatment.

action in the height of the adenoma, but no further shrinkage was documented afterward (Fig. 5). In patient 7 treatment with octreotide produced a pronounced inhibition of GH and TSH secretion during 1 yr, whereas the serum α-subunit concentration was only slightly reduced.

Discussion

TSH-secreting pituitary adenomas are rarely encountered and represent about 1% of all pituitary adenomas. About 80 cases have so far been described (1–3). We report here a series of 7 cases from a total of 800 pituitary adenomas studied during the last 15 yr. All of our patients were documented with clinical and biological hyperthyroidism. The frequency and sex ratio of TSH-secreting adenomas in our series conform to the data from the literature. With the exception of the 84-yr-old patient, the age range is similar to that previously reported of 17–64 yr. That most patients with TSH-secreting tumors presented with macroadenomas is confirmed in our series.

In our series basal serum TSH levels were between 1.1–36.3 mU/L, which is in accordance with the range of 1.5–568 mU/L mentioned by other researchers (1–3). In cases of elevated serum thyroid hormone concentrations with high serum TSH levels, the α-subunit/TSH molar ratio is commonly used to differentiate between TSH-secreting pituitary adenomas (ratio above unity) and selective pituitary resistance to thyroid hormones (ratio below unity). An aberrant ratio in the presence of TSH-secreting adenomas is only mentioned three times in the literature, but the data from the first report are not available (1). In the second report an euthyroid patient with elevated serum TSH and FSH levels and a pituitary adenoma was presented, but immunocytochemistry of the adenoma was only positive for FSH (8). The third patient was primarily described as having a TSH-secreting adenoma (9), but since the ratio was supposed to be erroneously calculated, it was afterward presented as a feedback tumor following thyroidectomy (1). The extremely low ratio found in patient 2 is due to the absence of serum α-subunit. It is the first primary TSH-secreting pituitary adenoma with hyperthyroidism where TSH secretion was not accompanied by α-subunit cosecretion. The molar ratio remains a good discriminating factor for the diagnosis of TSH-secreting adenoma, but more exceptions such as our patient may hamper the clinical picture in the future.

Study of circadian rhythm in two patients revealed similar profiles for TSH and α-subunit secretion. In the first case an inverted rhythm for TSH was observed, with an acrophase in the middle of the day and a nadir during the night, in contrast to the pattern in normal subjects. In the other case no apparent rhythmicity of TSH or α-subunit was recorded, but in this acromegalic patient the classic GH secretory pattern was maintained. In one case the secretion of α-subunit appeared to follow a pulsatile pattern, which is not the case for TSH. This

Fig. 5. Frontal T₁-weighted MR imaging of pituitary region in a patient (no. 6) with a TSH-secreting pituitary adenoma treated with octreotide (A, before treatment; B, after 6 months of treatment).
dissociation does not seem to be due to an interference with the LH pulsatility, since the peaks of LH and α-subunit were not simultaneously recorded. The pulsatility of α-subunit and TSH was also studied in another case (10). In this patient without circadian rhythmicity, 7 TSH and 13 α-subunit pulses were revealed over a 24-h period. The loss of a diurnal pattern for TSH was also observed in another patient (3).

TRH could not stimulate TSH in 77% of all TSH-secreting adenomas (1, 2), but opposite findings were also recorded (3). In our series a TSH response was found in 4 patients, but the increase exceeded 100% of basal values in only 1 case. It is obvious that the presence of a TSH response to TRH cannot be used as an excluding criterion in the diagnosis of TSH-secreting adenoma. In 1 case we found a paradoxical response of TSH to GnRH. Our series also confirms the unresponsiveness of TSH to T₄ suppression (84% in the literature) and the responsiveness to antithyroid drug administration (70% in the literature). It is, however, unclear whether the elevation in serum TSH in response to methimazole administration is due to increased secretion by the normal or adenomatous thyrotrphs. In contrast, the suppression of TSH by dexamethasone (present in 11 of 12 cases) was not observed in 2 of our patients. The rather poor suppression of TSH secretion by dopamine agonists reported previously (absent in 24 of 31 cases) was also observed in our series.

Concomitant secretion of hormones besides TSH and α-subunit by TSH-secreting adenomas is well recognized. Hypersecretion of GH is the most frequently encountered association. It was mentioned in 18 patients in the review of Smallridge (2) and in 19 of 76 patients in the review of Foglia et al. (1). Since then, cosecretion was reported in other patients (3, 11, 12). We add 3 more cases in which an acromegalic syndrome accompanied the TSH-secreting adenoma. In 1 patient it was the cardinal feature at presentation. Hyperprolactinemia is less frequently present. It was mentioned in 13 cases in the review by Smallridge (2) and in 7 cases in the review of Foglia et al. (1). Recently, a higher incidence of hyperprolactinemia was reported in the series of Gesundheit et al. (3), where it was present in 7 of 9 patients. It is unclear if hyperprolactinemia represents cosecretion or only hypothalamic dysregulation, since the serum PRL levels are in most cases only slightly elevated and sometimes respond normally to TRH. The elevated serum PRL concentration was confirmed by positive immunostaining for PRL in only 4 reports (13–16). In another case in vitro secretion of PRL was present, but immunostaining was negative (17). We add 3 more patients with hyperprolactinemia, all nonresponsive to TRH and 2 with positive immunostaining for PRL. To our knowledge, we report the only patient in whom cosecretion of TSH, GH, and PRL was proven by elevated serum levels and immunostaining. This patient was also the only subject without α-subunit secretion. Only 1 earlier report mentioned the elevation of both serum GH and PRL levels in the presence of a TSH- and α-subunit-secreting adenoma (18). Since the PRL secretion responded normally to stimulatory and inhibitory tests and since the immunostaining was negative for PRL, it is probable that the hyperprolactinemia was due to a diminished hypothalamic inhibition.

Neurosurgery is the treatment of choice for TSH-secreting pituitary adenomas. Nevertheless, the literature mentions a rate of success of only 31% (19 of 62 patients), reaching 42% when combined with radiotherapy (1). Three of 4 patients who underwent transsphenoidal adenomectomy in our center were considered cured, although 1 presented a recurrence after 5 yr. Surgery could not cure the other 2 patients. Medical adjunctive treatment is, thus, necessary to control pituitary tumor growth and hormonal secretion. The presence of somatostatin receptors in TSH-secreting adenomas allowed consideration of long term treatment with a long-acting somatostatin analog (19). Until now, 10 TSH-secreting adenomas treated with octreotide were reported previously (11, 12, 20–23). All responded with an important suppression of serum TSH levels, except for 1 case (21), while in another case an escape from treatment for TSH and α-subunit, but not GH, was noticed (11). Inhibition of GH secretion in 3 patents (11, 12, 22) and PRL secretion in another patient (20) was also recorded. These promising results obtained by long term octreotide administration were confirmed in our 3 patients. In 1 of them, however, tachyphylaxis was observed after 6 months of treatment, not only for TSH and α-subunit but also for GH. Long term treatment with octreotide is also capable of reducing the size of the adenoma, as demonstrated by CT scanning (4, 23), MR imaging, and visual perimetry (20).

Acknowledgments
We are indebted to Dr. Alan G. Harris (Sandoz Ltd., Basel, Switzerland) and Dr. M. de Longueville (Sandoz Ltd., Brussels, Belgium) for supplying octreotide.

References


